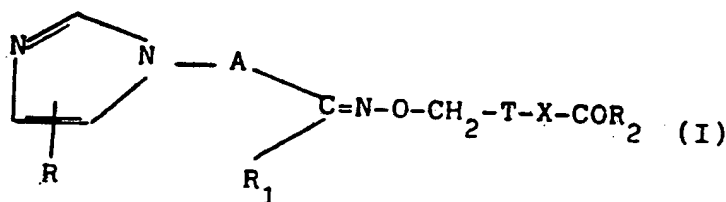




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(54) Title: SUBSTITUTED 1-(ALKOXY-IMINOALKYL)IMIDAZOLE DERIVATIVES



(57) Abstract

1-(Alkoxy-iminoalkyl)imidazole derivatives of formula (I), wherein R is hydrogen or C₁-C₄ alkyl; A is C₁-C₄ alkylene optionally substituted by phenyl optionally substituted by halogen or trifluoromethyl; R is (a) hydrogen or a C₁-C₁₀ hydrocarbon radical; (b) an aryl or aryl-C₁-C₄ alkyl group wherein the said aryl is optionally substituted either by halogen, trihalomethyl, C₁-C₄ alkyl, C₂-C₃ alkenyl, C₂-C₆ alkynyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio or C₁-C₄ alkylsulfonyl or by C₅-C₈ alkyl, C₄-C₈ alkenyl, C₅-C₈ alkoxy, C₅-C₈ alkylthio or phenyl optionally substituted by halogen, trihalomethyl or C₁-C₄ alkyl; or (c) a C₅-C₈ cycloalkyl or C₅-C₈ cycloalkyl-C₁-C₄ alkyl group, wherein the said cycloalkyl is optionally substituted by C₁-C₄ alkyl; T is a C₁-C₆ hydrocarbon chain or phenylene; X is a bond, -O-CH₂-, -C(R' R'')-, Si(R' R'')-, vinylene or isopropenylene, each R' and R'' being hydrogen, fluorine or C₁-C₄ alkyl; and R₂ is -OR₃ or -N(R₃R₄), each R₃ and R₄ being hydrogen, C₁-C₆ alkyl, phenyl or benzyl; and the pharmaceutically acceptable salts thereof; are useful in the treatment of a disease state related to enhancement of thromboxane A₂ (TxA₂) synthesis.

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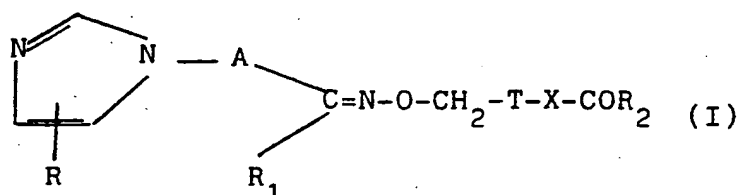
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SUBSTITUTED 1-(ALKOXY-IMINOALKYL)IMIDAZOLE DERIVATIVES

The present invention relates to new 1-(alkoxy-iminoalkyl) imidazole derivatives, to a process for their preparation, to pharmaceutical compositions containing them and to their use as therapeutic agents.

The present invention provides novel compounds having the general formula (I)



wherein

10 R is hydrogen or C_1-C_4 alkyl;

A is a C_1-C_4 alkylene chain unsubstituted or substituted by a phenyl ring unsubstituted or substituted by one or two substituents chosen independently from halogen and trifluoromethyl;

15 R_1 is a) hydrogen or a straight or branched, saturated or unsaturated C_1-C_{10} hydrocarbon radical; b) an aryl or aryl- C_1-C_4 alkyl group, wherein the aryl group or the aryl moiety is unsubstituted or substituted either by one to four substituents independently chosen from halogen, trihalomethyl, C_1-C_4 alkyl, C_2-C_3 alkenyl, C_2-C_6 alkynyl, C_1-C_4

20 alkoxy, C_1-C_4 alkylthio and C_1-C_4 alkylsulfonyl or by a substituent chosen from C_5-C_8 alkyl, C_4-C_8 alkenyl,

C_5-C_8 alkoxy, C_5-C_8 alkylthio and phenyl, in which

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the phenyl ring is unsubstituted or substituted by a substituent chosen from halogen, trihalomethyl and C_1-C_4 alkyl; or (c) a C_5-C_8 cycloalkyl or C_5-C_8 cycloalkyl- C_1-C_4 alkyl group, wherein the cycloalkyl group or moiety is unsubstituted or substituted by one to three C_1-C_4 alkyl groups;

T is a straight or branched, saturated or unsaturated C_1-C_6 hydrocarbon chain, or a phenylene radical;

X is a bond or a divalent group consisting of $-O-CH_2-$, $-C(R' R'')-$, $-Si(R' R'')-$, vinylene or isopropenylene, wherein each of R' and R'' being the same or different is hydrogen, fluorine or C_1-C_4 alkyl;

R_2 is an $-OR_3$ or $-N(R_3 R_4)$ group, wherein each of R_3 and R_4 independently is hydrogen, C_1-C_6 alkyl, phenyl or benzyl; and the pharmaceutically acceptable salts thereof.

The invention also includes within its scope all the possible isomers, stereoisomers and their mixtures and the metabolites and the metabolic precursors or bioprecursors of the compounds of formula (I).

In particular the compounds of formula (I) exhibit either E or Z isomerism about the oximic double bond. Both the single E and Z isomers of the compounds of formula (I) and their mixtures are also included within the scope of the present invention.

The alkylene chain A may be, independently, a straight or branched chain, unsubstituted or substituted, as defined above.

Typically $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $>CH-CH_3$, $>CH-CH_2-Ph$, $-CH_2-CH(Ph)-$, $>CH-CH_2-CH_2-Ph$, $>CH-CH(CH_3)-CH_2Ph$, $CH_2-CH(CH_2Ph)-$ and $-CH-CH_2-CH(CH_3)-Ph$, wherein Ph represents a phenyl ring as defined above.

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When R_1 is a C_1-C_{10} hydrocarbon radical as defined above under a), it is preferably a C_1-C_8 alkyl or C_2-C_9 alkenyl radical, for example C_2-C_8 alkenyl, in particular pentyl, hexyl and heptyl or propenyl and butenyl, respectively.

- 5 When R_3 and/or R_4 is a C_1-C_6 alkyl group it is, e.g., methyl, ethyl, propyl, isopropyl, butyl or tert.butyl, more preferably methyl or ethyl.

When R_1 is an aryl or arylalkyl group as defined above under b), the aryl group or the aryl moiety may be an aromatic or
10 heteroaromatic group, for example phenyl, pyridyl, thienyl and naphthyl, in particular phenyl, pyridyl and thienyl.

According to the definition of R_1 as an aryl or arylalkyl group given hereabove, a pyridyl group is preferably a 2- or 3-pyridyl group; a thienyl group is preferably a 2-thienyl
15 group and a naphthyl group is preferably a 1- or 2-naphthyl group.

Accordingly, an arylalkyl group, as defined above, is preferably a phenyl-, thienyl- or pyridyl- C_1-C_2 alkyl group, in particular a benzyl, thienylmethyl or pyridylmethyl group.

- 20 When R_1 is a cycloalkyl or cycloalkyl-alkyl group as defined above under c), the cycloalkyl group or the cycloalkyl moiety is preferably a cyclohexyl or cycloheptyl group.

Accordingly, a cycloalkyl-alkyl group, as defined above, is preferably a cyclohexyl- or cycloheptyl- C_1-C_2 alkyl group, in
25 particular cyclohexylmethyl or cycloheptylmethyl.

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When T is a hydrocarbon chain it is preferably an alkylene or alkenylene, radical, for example a C_1-C_5 alkylene chain, in particular $-CH_2-$, $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$ or a C_2-C_5 alkenylene chain, in particular $-CH=CH-$, $-CH_2-CH=CH-$ or $-CH=CH-CH_2-$.

When T is a phenylene radical, it is e.g. a 1,2-, 1,3- or 1,4-phenylene, in particular a 1,3-phenylene radical.

The alkyl, alkoxy, alkylsulfonyl and alkylthio groups may be branched or straight chain groups.

10 A C_1-C_4 alkyl group is e.g. methyl, ethyl, propyl, isopropyl, butyl or tert. butyl, more preferably methyl or butyl.

A C_1-C_4 alkoxy group is e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy or tert. butoxy, preferably methoxy, ethoxy or propoxy.

15 A C_1-C_4 alkylthio group is e.g. methylthio, ethylthio, propylthio or butylthio, in particular methylthio or ethylthio.

A C_5-C_8 alkyl group is preferably hexyl or heptyl.

A C_2-C_3 alkenyl group is preferably ethenyl.

20 A C_4-C_8 alkenyl group is preferably butenyl or hexenyl.

A C_2-C_6 alkynyl group is preferably a C_2-C_4 alkynyl group in particular ethynyl.

A C_5-C_8 alkoxy group is preferably pentyloxy or hexyloxy.

A C_5-C_8 alkylthio group is preferably pentylthio or hexylthio.

25 A halogen atom is suitably bromine, chlorine or fluorine, preferably it is bromine or fluorine.

A C_1-C_4 alkylsulfonyl group is preferably a methyl- or ethylsulfonyl, in particular methylsulfonyl, group.

30 A trihalomethyl group is e.g. trichloromethyl or trifluoromethyl, in particular trifluoromethyl.

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Pharmaceutically acceptable salts of the compounds of the invention include acid addition salts, with inorganic, e.g. nitric, hydrochloric, hydrobromic, sulphuric, perchloric and phosphoric acids, an organic, e.g. acetic, propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic and salicylic acids, and salts with inorganic, e.g. alkali metal, especially sodium or potassium, bases or alkaline-earth metal, especially calcium or magnesium, bases, or with organic bases, e.g. alkylamines, preferably triethyl-amine.

As stated above the present invention also includes within its scope pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I), i.e. compounds which have a different formula to formula (I) above but which nevertheless upon administration to a human being are converted directly or indirectly in vivo into a compound of formula (I).

Preferred compounds of the invention are the compounds of formula (I), wherein,

R is hydrogen or methyl;

A is a C_1-C_4 alkylene chain optionally substituted by phenyl, in its turn optionally substituted by one or two substituents independently chosen from halogen and trifluoromethyl;

R_1 is a) C_1-C_8 alkyl or C_2-C_8 alkenyl; b) a phenyl, naphthyl, thienyl or pyridyl group unsubstituted or substituted either by one or two substituents independently chosen from halogen, trihalomethyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl and C_1-C_4 alkylthio, or by a substituent chosen from C_5-C_8 alkyl, C_4-C_8 alkenyl, C_5-C_8 alkoxy, C_5-C_8 alkylthio and phenyl,

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- in which the phenyl ring is unsubstituted or substituted by a substituent chosen from halogen, trihalomethyl and C_1-C_4 alkyl; or (c) a cyclohexyl or cycloheptyl group unsubstituted or substituted by one or two C_1-C_4 alkyl groups;
- 5 T is a C_1-C_5 alkylene or C_2-C_5 alkenylene group; or a phenylene group;
- X is a bond or a $-O-CH_2-$ group;
- R_2 is an $-OR_3$ or $-NHR_3$ group, wherein R_3 is hydrogen or C_1-C_4 alkyl; and the pharmaceutically acceptable salts thereof.
- 10 More preferred compounds of the invention are the compounds of formula (I), wherein,
- R is hydrogen;
- A is $-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-$ or $-CH(CH_2Ph)-$ in which Ph means phenyl optionally substituted by a halogen atom;
- 15 R_1 is a) C_5-C_7 alkyl; b) a phenyl, pyridyl or thienyl ring, unsubstituted or substituted by halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or trifluoromethyl; or c) a cyclohexyl or cycloheptyl ring;
- T is a C_2-C_4 alkylene or phenylene group;
- 20 X is a bond or a $-O-CH_2-$ group;
- R_2 is an $-OR_3$ group wherein R_3 is hydrogen or C_1-C_4 alkyl; and the pharmaceutically acceptable salts thereof.

- Examples of specific compounds according to the present invention are the following compounds, either as Z or
- 25 E-isomers or Z, E-mixtures of said isomers;

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- 1) 5-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- 2) 5-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanamide;
- 5 3) ethyl 4-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoate;
- 4) 4-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- 5) methyl 3-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoate;
- 10 6) ethyl 5-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoate;
- 7) 5-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- 15 8) 5-[1-(3-bromophenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- 9) 4-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- 10 10) 5-[1-(3-(n-butyl)phenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- 11) 5-[1-(2-methoxyphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- 12) ethyl 3-oxa-5-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoate;
- 25 13) 3-oxa-5-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- 14) 3-oxa-5-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- 15) tert-butyl 5-[1-phenyl-2-(imidazol-1-yl)-2-methyl-ethylidene]aminoxypentanoate;
- 30

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- 16) 5-[1-phenyl-2-(imidazol-1-yl)-2-methylethylidene]-
aminoxypentanoic acid;
- 17) 3-[1-phenyl-2-(imidazol-1-yl)ethylidene]
aminoxymethylbenzoic acid;
- 5 18) 4-[1-phenyl-3-(imidazol-1-yl)propylidene]aminoxy-
butanoic acid;
- 19) 5-[1-(n-hexyl)-2-(imidazol-1-yl)ethylidene]aminoxy-
pentanoic acid;
- 20) ethyl 5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]
10 aminoxypentanoate;
- 21) tert-butyl 5-[1-cyclohexyl-2-(imidazol-1-yl)ethyli-
dene]aminoxypentanoate;
- 22) 5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]amino-
xypentanoic acid;
- 15 23) ethyl 4-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]
aminoxybutanoate;
- 24) 4-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]
aminoxybutanoic acid;
- 25) 5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]
20 aminoxypentanamide;
- 26) 3-oxa-5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]
aminoxypentanoic acid;
- 27) 5-[1-(3,3-dimethylcyclohexyl)-2-(imidazol-1-yl)
ethylidene] aminoxypentanoic acid;
- 25 28) 5-[1-cyclopentyl-2-(imidazol-1-yl)ethylidene]
aminoxypentanoic acid;
- 29) 5-[1-(2-thienyl)-2-(imidazol-1-yl)ethylidene]
aminoxypentanoic acid;
- 30) ethyl 5-[1-(3-pyridyl)-2-(imidazol-1-yl) ethylidene]
30 aminoxypentanoate;
- 31) 5-[1-(3-pyridyl)-2-(imidazol-1-yl)ethylidene]
aminoxypentanoic acid;
- 32) 4-[1-(3-pyridyl)-2-(imidazol-1-yl)ethylidene]
aminoxybutanoic acid;

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- 33) 5-[1-(3-n-butyloxyphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- 34) ethyl 5-[1-(3-n-butyloxyphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoate;
- 5 35) 6-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]aminoxihexanoic acid;
- 36) 3-oxa-6-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]aminoxihexanoic acid;
- 37) 5-[1-cycloheptyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- 10 38) 6-[1-cycloheptyl-2-(imidazol-1-yl)ethylidene]aminoxihexanoic acid;
- 39) 5-[1-n-heptyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- 15 40) 5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoic acid;
- 41) 5-[1-cyclohexyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoic acid;
- 42) ethyl 5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoate;
- 20 43) ethyl 5-[1-cyclohexyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoate;
- 44) 6-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxihexanoic acid;
- 25 45) 6-[1-cyclohexyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxihexanoic acid;

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- 46) 5-[1-(4-fluorophenyl)-2-(imidazol-1-yl)-2-(4-fluorobenzyl) ethylidene] aminoxypentanoic acid;
- 47) 5-[1-cyclohexyl-2-(imidazol-1-yl)-2-(4-fluorobenzyl) ethylidene] aminoxypentanoic acid; and
- 5 48) 3-oxa-5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene] aminoxypentanoic acid;
- and the pharmaceutically acceptable salts thereof.


Table A

No.	A	R ₁	T	X	R ₂
1	-CH ₂ -	Ph	-(CH ₂) ₃ -	bond	OH
2	-CH ₂ -	Ph	-(CH ₂) ₃ -	bond	NH ₂
3	-CH ₂ -	Ph	-(CH ₂) ₂ -	bond	OEt
4	-CH ₂ -	Ph	-(CH ₂) ₂ -	bond	OH
5	-CH ₂ -	Ph	-CH ₂ -	bond	OMe
6	-CH ₂ -	(3CF ₃)Ph	-(CH ₂) ₃ -	bond	OEt
7	-CH ₂ -	(3CF ₃)Ph	-(CH ₂) ₃ -	bond	OH
8	-CH ₂ -	(3Br)Ph	-(CH ₂) ₃ -	bond	OH
9	-CH ₂ -	(3CF ₃)Ph	-(CH ₂) ₂ -	bond	OH
10	-CH ₂ -	(3nBu)Ph	-(CH ₂) ₃ -	bond	OH
11	-CH ₂ -	(2OCH ₃)Ph	-(CH ₂) ₃ -	bond	OH
12	-CH ₂ -	Ph	-CH ₂ -	-OCH ₂ -	OEt
13	-CH ₂ -	Ph	-CH ₂ -	-OCH ₂ -	OH
14	-CH ₂ -	(3CF ₃)Ph	-CH ₂ -	-OCH ₂ -	OH
15	-CH(CH ₃)-	Ph	-(CH ₂) ₃ -	bond	OtBu
16	-CH(CH ₃)-	Ph	-(CH ₃) ₃ -	bond	OH

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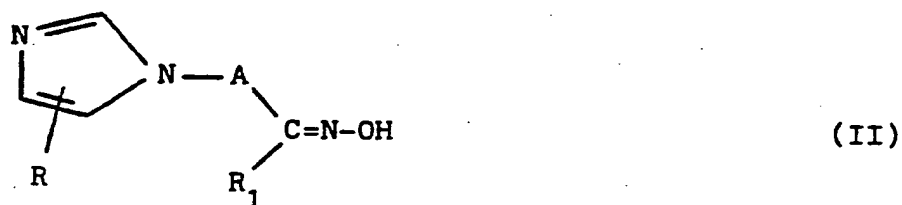
No.	A	R ₁	T	X	R ₂
17	-CH ₂ -	Ph		bond	OH
18	-(CH ₂) ₂	Ph	-(CH ₂) ₂ -	bond	OH
19	-CH ₂ -	n-hexyl	-(CH ₂) ₃ -	bond	OH
20	-CH ₂ -	cyclohexyl	-(CH ₂) ₃ -	bond	OEt
21	-CH ₂ -	cyclohexyl	-(CH ₂) ₃ -	bond	OtBu
22	-CH ₂ -	cyclohexyl	-(CH ₂) ₃ -	bond	OH
23	-CH ₂ -	cyclohexyl	-(CH ₂) ₂ -	bond	OEt
24	-CH ₂ -	cyclohexyl	-(CH ₂) ₂ -	bond	OH
25	-CH ₂ -	cyclohexyl	-(CH ₂) ₃ -	bond	NH ₂
26	-CH ₂ -	cyclohexyl	-CH ₂ -	-OCH ₂ -	OH
27	-CH ₂ -	(3,3-di-Me) cyclohexyl	-(CH ₂) ₃ -	bond	OH
28	-CH ₂ -	cyclopentyl	-(CH ₂) ₃ -	bond	OH
29	-CH ₂ -	2-thienyl	-(CH ₂) ₃ -	bond	OH
30	-CH ₂ -	3-pyridyl	-(CH ₂) ₃ -	bond	OEt
31	-CH ₂ -	3-pyridyl	-(CH ₂) ₃ -	bond	OH
32	-CH ₂ -	3-pyridyl	-(CH ₂) ₂ -	bond	OH

No.	A	R ₁	T	X	R ₂
33	-CH ₂ -	(3nBuO)Ph	-(CH ₂) ₃ -	bond	OH
34	-CH ₂ -	(3nBuO)Ph	-(CH ₂) ₃ -	bond	OEt
35	-CH ₂ -	cyclohexyl	-(CH ₂) ₄ -	bond	OH
36	-CH ₂ -	cyclohexyl	-(CH ₂) ₂ -	-OCH ₂ -	CH
37	-CH ₂ -	cycloheptyl	-(CH ₂) ₃ -	bond ²	OH
38	-CH ₂ -	cycloheptyl	-(CH ₂) ₄ -	bond	OH
39	-CH ₂ -	n-heptyl	-(CH ₂) ₃ -	bond	OH
40	-CH(PhCH ₂)-	Ph	-(CH ₂) ₃ -	bond	OH
41	-CH(PhCH ₂)-	cyclohexyl	-(CH ₂) ₃ -	bond	OH
42	-CH(PhCH ₂)-	Ph	-(CH ₂) ₃ -	bond	OEt
43	-CH(PhCH ₂)-	cyclohexyl	-(CH ₂) ₃ -	bond	OEt
44	-CH(PhCH ₂)-	Ph	-(CH ₂) ₄ -	bond	OH
45	-CH(PhCH ₂)-	cyclohexyl	-(CH ₂) ₄ -	bond	OH
46	-CH(4-F-PhCH ₂)-	4-F-Ph	-(CH ₂) ₃ -	bond	OH
47	-CH(4-F-PhCH ₂)-	cycloheyl	-(CH ₂) ₃ -	bond	OH
48	-CH(PhCH ₂)-	Ph	-CH ₂ -	-OCH ₂ -	OH

In the above table Ph means phenyl; Me means methyl; Et means ethyl; and Bu means butyl.

The compounds of the invention and the salts thereof can be obtained by a process comprising:

a) reacting an oxime of formula (II) or a salt thereof



5 wherein

R, A and R_1 are as defined above, with a compound of formula (III)



wherein

10 T, X and R_2 are as defined above and Y is a leaving group; or

b) reacting an oxime of formula (II) as defined above or a salt thereof with a lactone of formula (IV)

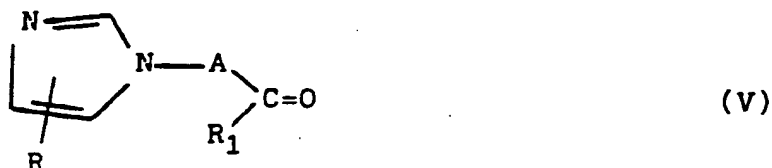


15 wherein

T and X are as defined above, thus obtaining a compound of formula (I) in which R_2 is -OH; or

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c) reacting a compound of formula (V)



wherein

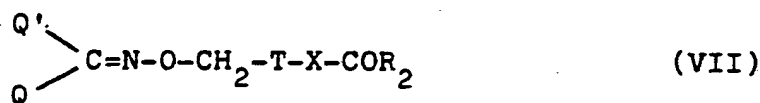
R, A and R₁ are as defined above, with a compound of formula
 5 (VI)



wherein

T, X and R₂ are as defined above; or

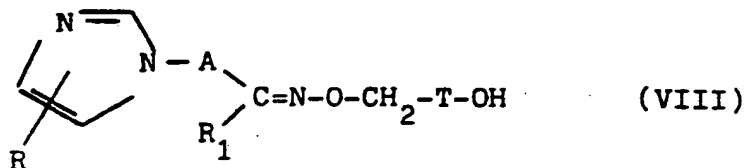
d) reacting a compound of formula (V), as defined above,
 10 with a compound of formula (VII)



wherein

T, X and R₂ are as defined above and each of Q and Q' is
 independently hydrogen, lower alkyl or phenyl; or

e) reacting a compound of formula (VIII) or a salt thereof
 15



wherein

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R, R₁, A and T are as defined above, with a compound of formula (IX)



wherein

- 5 Y and R₂ are as defined above, thus obtaining a compound of formula (I) wherein X is a -O-CH₂- group; and if desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired converting a compound of formula (I) into a salt thereof, and/or, if desired, converting a salt of a compound of formula (I) into a free compound, and/or, if desired, separating a mixture of isomers of a compound of formula (I) into the single isomers, and/or, if desired, altering by isomerization on the oxime double bond the ratio of E- and Z-isomers of a compound of formula (I) in a mixture thereof so as to obtain a different ratio of such isomers, and/or, if desired, converting by isomerization on the oxime double bond a pure E-isomer of a compound of formula (I) either into a pure Z-isomer thereof or into a mixture of E- and Z-isomers thereof; and/or if desired converting by isomerization on the oxime double bond a pure Z-isomer of a compound of formula (I) either into a pure E-isomer or into a mixture of E- and Z-isomers thereof.

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A salt of a compound of formula (II) is for example an alkali metal salt, in particular a sodium or lithium salt. A salt of a compound of formula (II) may be obtained according to known methods, for example a compound of formula (II) can be reacted with an alkali metal hydride, preferably NaH, in an inert organic solvent, e.g. dimethylformamide.

The leaving group Y in a compound of formula (III) is for example an halo group, in particular a chloro or bromo group, or a residue of an active ester group, in particular mesyl or tosyl.

The reaction of a compound of formula (II), or a salt thereof, with a compound of formula (III) can be carried out according to known methods, for example in the presence of an inert reaction organic solvent e.g. dimethylformamide, dimethylsulfoxide, tert. butanol or benzene, and by addition of an appropriate basic agent e.g. an alkali metal carbonate, in particular sodium carbonate, or sodium hydride or potassium tert. butylate, at a temperature ranging from about 0°C to reflux temperature.

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The reaction of a compound of formula (II) or a salt thereof, as defined above, with a compound of formula (IV) may be performed according to known methods. For

5 example such reaction can be carried out by following the same reaction conditions described as to the reaction of a compound of formula (II), or a salt thereof, with a compound of formula (III).

10 The reaction of a carbonyl compound of formula (V) with an aminoxy derivative of formula (VI) can be carried out for example, by dissolving the carbonyl compound in a reaction inert solvent e.g. water, a lower alkanol in particular ethanol, dioxane, tetrahydrofuran, an aromatic hydrocarbon in particular benzene, toluene or xylene, or mixtures of such solvents, and by adding an
15 appropriate basic agent, for example an alkali metal hydroxide in particular sodium or potassium hydroxide, a carbonate or hydrogen carbonate in particular the sodium and potassium ones, or an organic basic agent e.g. a tertiary amine or pyridine.

20 When one or both of Q and Q' in a compound of formula (VII) is lower alkyl, it is for example C₁-C₄ alkyl in particular methyl or ethyl.

Also the reaction of a compound of formula (V) with a compound of formula (VII) can be carried out according
25 to known methods. For example such reaction can be performed in an inert reaction solvent e.g. acetonitrile or acetic acid, and if required in the presence of a mineral acid e.g. sulphuric or

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hydrochloric acid, at temperatures ranging from room temperature to reflux temperature.

A salt of a compound of formula (VIII) is for example an alkali metal salt, in particular a sodium or lithium salt.

The leaving group Y in a compound of formula (IX) is for example a halo group, in particular a chloro or bromo group, or a residue of an active ester group, in particular mesyl or tosyl.

The reaction of a compound of formula (VIII), or a salt thereof, with a compound of formula (IX) can be carried out by following the same reaction conditions described above as to the reaction of a compound of formula (II), or a salt thereof, with a compound of formula (III).

The conversion of a compound of formula (I) into another compound of formula (I) can be carried out by methods known in themselves. For example, a compound of formula (I) containing an esterified carboxy group can be converted into the corresponding free carboxylic acid by known methods. In particular a compound of formula (I) in which R_2 is an OR_3 group wherein R_3 , being as defined above, is other than hydrogen can be converted by acidic or alkaline hydrolysis into the respective free carboxylic acid. The reaction is preferably

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carried out at temperatures ranging from about -5°C to about 50°C .

A compound of formula (I) containing a free carboxy group, such as a compound of formula (I) in which R_2 is hydroxy, can be converted into a corresponding esterified carboxy derivative, e.g. a compound of formula (I) in which R_2 is an $-\text{OR}_3$ group, wherein R_3 , being as defined above, is other than hydrogen. Such esterification reaction can be carried out according to known methods, preferably via an intermediate reactive derivative of the carboxylic acid, which may be isolated or not, by reaction with the appropriate alcohol of formula R_3OH , in which R_3 being as defined above, is other than hydrogen. The reaction can be carried out in a customary solvent e.g. benzene or toluene, or in the presence of an excess of the alcohol itself of formula R_3OH .

The temperature reaction may range from about 10°C to about 50°C . Intermediate reactive derivatives of the carboxylic acid may be for example acidic halides, e.g. the chloride, mixed anhydrides e.g. ethoxycarbonyl or tert. butyloxy anhydrides, or a suitable reactive intermediate obtained in situ e.g. by reaction with a diimide e.g., dicyclohexylcarbodiimide, or carbonyl diimidazole.

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A compound of formula (I) wherein R_2 is hydroxy, i.e. containing a free carboxy group, can be converted into a corresponding compound of formula (I) wherein R_2 is a $-NR_3R_4$ group, in which R_3 and R_4 are as defined above, according to known methods; preferably via an intermediate reactive derivative thereof, which can be isolated or not.

Intermediate reactive derivatives may be active esters e.g. NO_2 -phenyl esters, or N-hydroxysuccinimide esters, acid halides, preferably chloride, mixed anhydrides e.g. ethoxycarbonyl or tert-butylcarbonyl anhydrides, or the reactive intermediates obtained in situ by reaction of the acid with dicyclohexylcarbodiimide or carbonyldiimidazole.

For example, a reactive intermediate as defined above, which can be obtained following conventional ways, as those usually employed in the synthesis of peptides, is reacted with ammonia or an appropriate amine in a customary solvent or with an excess of the amine itself at temperatures ranging from about $-10^\circ C$ to about $50^\circ C$.

The optional salification of a compound of formula (I) as well as the conversion of a salt into the free compound and the separation of a mixture of isomers into the single isomers may be carried out by conventional methods.

For example the separation of a mixture of geometric isomers, e.g. Z- and E-isomers, may be carried out by fractional crystallization from a suitable solvent or by chromatography, either column chromatography or high pressure liquid chromatography.

The optional isomerization on the oxime double bond in a compound of formula (I), which is an equilibrium reaction, can be performed according to known methods; preferably in the presence of a mineral acid e.g. hydrochloric acid and/or by heating.

The oximes of formula (II) can be obtained according to known methods. For example a') by reaction of a compound of formula (V), as defined above, with hydroxylamine or an acid addition salt thereof, e.g. the sodium or potassium salt, or b') by reaction of an oxime of formula (X)



wherein Y, A and R₁ are as defined above, with imidazole, C₁-C₄ alkyl imidazole or a salt thereof, e.g. following for example the procedure in *Arzneim.Forsch./Drug Res.*, 29(II), 1510-13, (1979).

In view of the oxime double bond, also an oxime of formula (II) may be obtained either as pure Z or E isomer or as a mixture thereof. Also an oxime of formula (II), if desired, can be submitted to the same isomerizations on the oxime double bond described above

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as to a compound of formula (I), according to known methods. Similarly, a mixture of Z and E isomers of an oxime of formula (II) can be separated into the single isomers by following customary methods.

- 5 The compounds of formula (III), (IV) and (V) are either known compounds or can be obtained by known methods from known compounds. Also the compounds of formula (VI) are either known compounds or can be obtained from known compounds by following known methods, e.g. those described in Tetrahedron (1967), 23, 4441, or in
10 general described in Organic Functional Group Preparation, by S.R.Sandler and W.Karo, Vol. III, chapter X, Academic Press, (1972).

- The compounds of formula (VII) can be obtained by
15 reaction of a known compound of formula (XI)



wherein Q and Q' are as defined above, with a compound of formula (VI) as defined above, by following the same reaction procedures described above under process c).

- 20 Alternatively a compound of formula (VII) can be obtained from a compound of formula (XI), via the corresponding oxime of formula (XII)



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wherein Q and Q' are as defined above, by reaction either with a compound either of formula (III) or of formula (IV) by following the same reaction conditions described above under processes a) and b).

5 The compounds of formula (VIII) can be obtained from known compounds by following procedures similar to those described under processes a), b), c) and d) above.

10 When in the compounds of the invention and in the intermediate products thereof groups are present which need to be protected during the reactions reported above, the groups can be protected in conventional way before the reaction takes place and then deprotected after its end, according to well known methods.

15 PHARMACOLOGY

We have found that the compounds of formula (I), and the pharmaceutically acceptable salts thereof are selective inhibitors of thromboxane A_2 (TxA_2) synthesis and are therefore useful in the treatment of diseases related in particular to an enhancement of TxA_2 synthesis in mam-

20 mals, including humans.

The compounds of formula (I) were for example tested for their ability to inhibit TxA_2 Synthase activity (as reflected by TxB_2 generated in whole blood during clotting or in isolated glomeruli) in vitro in the rat.

25

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The in vitro experiments were carried out as follows:

The effect of the compounds on TxA_2 synthesis was evaluated in serum and in glomeruli isolated from kidney cortex of reduced renal mass rats (RRM). Ablation of $> 70\%$ of renal mass in the rat results in hypertension, proteinuria and glomerular sclerosis of the remnant kidney. Rats with a remnant kidney have increased excretion of thromboxane in the urine when compared with normal rats (Purkerson et al., Proc. Natl. Acad. Sci. USA 82, 193, 1985).

Blood was withdrawn from the abdominal aorta of the animals under light ether anesthesia. The blood was immediately divided in portions of 0.5 ml and distributed in glass tubes each containing a concentration of the test compounds or of the reference compounds, i.e. Dazoxiben, which is thromboxane synthase inhibitor (Randall et al. - Thromb. Res. 23, 145, 1981) and Acetylsalicylic acid (ASA), which is cyclooxygenase inhibitor.

Samples were then allowed to clot for 1 h at 37°C , centrifuged at 3000 rpm for 10 min, serum collected and stored at -20°C until assayed. TxB_2 levels were determined by RIA according to previously described procedures [Patrono et al. - Thromb. Res. 17, 3/4, 317, 1980] using highly specific antibody.

The isolation of glomeruli was performed as previously described [Patrignani et al., -J. Pharm. Exp. Ther. 228, 2, 472, 1984].

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The isolated glomeruli of 4 rats were pooled, suspended in modified Krebs buffer (pH 7.3) and divided into portions of 1 ml each containing a concentration of the test compounds or of the reference compounds.

5 The TxA_2 synthesis was induced by incubating the glomeruli under shaking at 37°C for 1 h. At that time the incubation was stopped by centrifugation at $+4^\circ\text{C}$, the supernatant collected and stored at -20°C until assayed by RIA.

10 The compounds of the invention showed remarkable activity in the above tests.

In particular for example, the compounds of the invention

(Z)-5-[1-cyclohexyl-2-(imidazol-1-yl)-ethylidene]amino-
15 xypentanoic acid (internal code FCE 26398), (+) (Z)-
-5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoic acid (FCE 27108) and (+) (E)-5-[1-phenyl-2-
-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoic acid
(FCE 27109), were found to exhibit a marked inhibitory
20 activity on TxA_2 synthesis significantly more potent than that of reference compounds Dazoxiben and ASA.

These results are summarized in Table 1.

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Table 1 - In vitro effects on TxB_2 production in whole blood and glomeruli of RRM rats. [Data are expressed as IC_{50} (M) and limits for $p=0.95$].

5	Compound	Whole Blood (n = 8)	Glomeruli (n = 6)
	FCE 26398	1.9×10^{-8} ($1.3-2.8 \times 10^{-8}$)	3.6×10^{-8} ($2.8-5.5 \times 10^{-8}$)
	FCE 27108	2.30×10^{-8} ($0.64-4.96 \times 10^{-8}$)	-----
10	FCE 27109	4.83×10^{-8} ($2.32-8.65 \times 10^{-8}$)	-----
	Dazoxiben	1.2×10^{-6} ($0.70-1.9 \times 10^{-6}$)	1.7×10^{-7} ($1.2-2.2 \times 10^{-7}$)
15	ASA	4.2×10^{-5} ($3.1-5.6 \times 10^{-5}$)	1.4×10^{-4} ($1.1-1.7 \times 10^{-4}$)

Wherein n is the number of replications.

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The compounds of the invention, being able to inhibit selectively the formation of TxA_2 , can be used as vasodilatory and antiaggregant agents, for example in all the cases of thrombosis, peripheral vasculopathies and coronary artery disease. In fact inhibition of TxA_2 production reduces the probability of thrombi formation and of vasoconstriction with consequent ischemic events and leaving unaltered (or increasing) PGI_2 production, improves vasodilation, tissue blood supplies and protects the vessel wall.

Moreover the compounds of the invention were tested for TxA_2 antagonism in a binding assay in washed human platelets, using as radiolabelled ligand $[\text{^3H}]\text{-SQ 29,548}$.

The experiments were carried out as follows:

Blood from healthy volunteers of both sexes who had no taken any medication for at least 10 days is collected into one-tenth volume of acid citrate dextrose containing indomethacin ($28 \mu\text{M}$). Platelet rich plasma (PRP), obtained by centrifugation of the blood at 200g for 20 min, is washed twice (1000g for 10 min). The platelets are then resuspended in Tyrode-Hepes buffer ($\text{pH } 7.4$) to a final concentration of $5\text{-}10 \times 10^8$ cells/ml and incubated for 0-60 min at 25° with $[\text{^3H}]\text{-SQ 29,548}$ (5 nM). For displacement experiments various concentrations (10^{-9} - 10^{-4}M) of competing ligands were added and incubated for 30 min at 25°C .

SUBSTITUTE SHEET

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Non-specific binding was determined in the presence of 50 μ M U46619 and was approximately 5% of total binding of $[^3\text{H}]\text{-SQ}$ 29,548. After the incubation, 4 ml of ice-cold TRIS-HCL buffer (10 mM, pH 7.4) was added to each tube and the reaction mixture was immediately filtered by suction through a Whatman GF/C glass filter disc which was washed 2 times with ice-cold TRIS-HCL (4 ml) and counted for radioactivity by a Packard- β -counter.

The binding data were analysed by computerized non-linear curve fitting using the Ligand program and expressed as IC_{50} . In Table II, as an example, the result obtained with the compound of the invention $(+)(\text{E})\text{-5-}[1\text{-phenyl-2-imidazol-1-yl})\text{-2-benzylethylidene}]$ aminoxypentanoic acid (code number FCE 27109) in the binding test is compared to that obtained with the reference standard compound Sulotroban (BM 13177) $[^3\text{H}]\text{-DE-A-2,809,377}$.

This result shows that the compound of the invention FCE 27109, besides being active as TxA_2 synthase inhibitor, has also a good affinity for the receptor better than that showed by the known compound Sulotroban (BM 13177), which on the other hand is devoid of TxA_2 synthase inhibitory activity.

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Table II - ^3H SQ 29,548 binding displacement (washed human platelets). IC_{50} (M).

BM 13177	7.3×10^{-6}
FCE 27109	1.9×10^{-7}

- 5 Being the compounds of the present invention both TxA_2 synthase inhibitors and PGA_2 (TxA_2)antagonists in the platelets on the basis of the state of the art, as reported e.g. in J. Clin. Invest. 80, 1435 (1987) and in Adm. Prostaglandins, Tromboxanes, Leukotrienes Res.
- 10 Vol. 17 (1987) p. 49, these compounds result particularly suitable for the treatment of a disease state in which an enhancement of TxA_2 synthesis exerts a pathogenic effect, for instance in those mentioned above.

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Another use of the compounds of the invention is for the treatment of migraine. As is known, for example, in the case of migraine it has been demonstrated a diffused vasoconstriction induced by platelet TxA₂ overproduction [J. Clin. Pathol. (1971), 24, 250; J. Headache (1977) 17, 101]. A platelet overproduction of TxA₂ and MDA (malondialdehyde) in diabetes mellitus has been demonstrated and correlated with microcirculatory defects in the illness [Metabolism (1979) 28, 394; Eu. J. Clin. Invest. (1979) 9, 223; Thrombosis Haemost. (1979), 42, 983; J. Lab. Clin. Med. (1981) 97, 87]. Therefore, the compounds of the invention can be used in the treatment of diabetes, in particular, diabetic microangiopathy.

Moreover, the compounds of the invention can be used as anti-inflammatory agents. As is known, for example, fluid obtained from carrageenin-induced granuloma converts arachidonic acid into TxA₂, in vitro and TxA₂ levels are increased in the synovial fluid of rheumatoid arthritis patients and in the fluid of carrageenin-induced inflammation in rats [Prostaglandins (1977), 13, 17; Scand. J. Rheum. (1977), 6, 151]. Recently it has been also demonstrated that an overproduction of TxA₂ is involved in the pathogenesis of hypertension and that a specific inhibitor of TxA₂ production may be employed in hypertension (Eu. J. Pharmacol. (1981), 70, 247]. In fact the compounds of the invention can be used as hypotensive agents.

For example an increased TxA_2 synthesis and decreased prostacyclin synthesis are reported in pregnancy-induced hypertension [Am. J. Obstet:Gynecol. (1987), 157, 325; Hypertension (1988), 11, 550]. Treatment with thromboxane synthase inhibitors is therefore useful in this pathology.

Furthermore it has been shown a role of TxA_2 in the pathogenesis of ulcerative disorders of the stomach in accordance with its powerful gastric vasoconstrictory activity, so that also in this field a TxA_2 inhibitor is useful [Nature (1981), 202, 472]. In fact the compounds of the invention are indicated for the treatment of peptic ulcers.

The compounds of the invention can be also antitumoral agents. It is known, for example, that a selective inhibition of TxA_2 synthesis has been demonstrated to reduce the number of lung metastases and to slow down tumor growth [Nature (1982), 295, 188].

In view of the correlation between TxA_2 synthesis and calcium transport, recently showed by some authors, specific TxA_2 synthetase inhibitors, such as the compounds of the invention, can also find use in the treatment of osteoporosis, e.g. post-menopausal osteoporosis [Prostaglandins (1981), 21, 401].

Moreover the compounds of the invention are indicated for the treatment of angina pectoris and heart failure. In

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this respect, it is known, for example, that high levels of TxB₂ have been found in patients with Prinzmetal's angina [Prostaglandins and Med. (1979), 2, 243] and in patients with recurrent angina attacks [Sixth Intern. Congress on Thrombosis, Monte Carlo October, 1980 Abs N° 140].

The platelet antiaggregatory activity of the compounds of the invention was evaluated in vitro and in vivo, for example, according to the modified methods of Born [Born G.V.R., Nature 194, 927 (1962)] and Silver [Silver M.J., Science 183, 1085 (1974)].

The compounds of this invention were found in vitro to have inhibitory activity on platelet aggregation induced by collagen or ADP (adenosine-5'-diphosphate) in platelet rich plasma of guinea pig [Dunkin Hantley Iva: PDH (SPF) Ivanovas GmbH, Germany].

Therefore the compounds of the invention may be useful in preventing or reducing platelet loss during extracorporeal circulation; for example during coronary artery bypass and graft procedures or during kidney dialysis. It has been moreover shown that circulatory shock, for example endotoxic and haemorrhagic shock, is associated with increased TxA₂ synthesis so that the compounds of the invention can be useful in these pathologies. Moreover, the compounds of the present invention can also be useful for the treatment of bronchial hyperreactivity in the therapy of asthma.

A role for TxA₂ in asthma can be inferred on the basis of its bronchoconstrictory activity in experimental animal models [Br. J. Pharmacol. (1984), 82 (3) 565]. An

inhibitory activity of bronchospasm induced by Platelet Activating Factor (PAF) in rats is also reported, e.g. for the TxA₂ synthetase inhibitors described in GB-B-2205494.

The compounds of the present invention can also find use in the treatment of nephropathies e.g. forms of glomerulonephritis, diabetic nephropathy or nephropathies secondary to systemic lupus erithematosus (SLE), and in the prevention and/or treatment of Cyclosporin A- induced nephrosis. Accordingly the compounds of this invention can also be used for preventing and/or treating toxemia during pregnancy, typically preeclampsia, eclampsia and preeclamptic (eclamptic, eclamptogenic) toxemia.

Recently a positive correlation between enhanced intrarenal synthesis of TxA₂ and the progression of chronic glomerular disease has been demonstrated in different animal models of immune and non-immune renal damage and in humans [J. Clin. Invest. (1985) 75, 94, J. Clin. Invest. (1985), 76, 1011].

Accordingly, the TxA₂ synthase inhibitors recently described e.g. in GB-B-2205240 were found to be active in reducing proteinuria and creatinine serum levels in the doxorubicin induced nephrosis in rats and in reducing

proteinuria and increasing the glomerular filtration rate (GFR) in the spontaneous focal glomerulosclerosis in the Milan Normotensive Strain (MNS) rats.

5 The compounds of the invention may be also used to inhibit the renal and cardiac transplant rejection. In fact after transplantation increased urinary TxB₂ excretion or whole blood TxA₂ synthesis have been reported both in man and rats [Lancet (1981), ii, 431; Transplantation (1987) 43, 346].

10 Another use of the compounds of the present invention is in the treatment of hyperlipidaemia, namely hypercholesterolaemia and hypertriglyceridaemia secondary to nephrotic syndrome.

15 Hyperlipidaemia is a common feature of nephrotic syndrome in man [New Engl. J. Med. (1983) 312 (24) 1544] and in addition elevated triglycerides and cholesterol levels are reported in animal models such as doxorubicin induced nephrotic syndrome [Expt. Mol. Pathology (1983), 39, 282]; elevated urinary albumin excretion has been suggested as the pathogenetic mechanisms [Kidney International (1987), 32, 813]. Also TxA₂ synthase inhibitors recently described in GB-B-2205240, e.g. proved to be active in reducing cholesterol and triglycerides in aged Milan Normotensive Strain rats and in reducing triglycerides in doxorubicin treated rats.

20

25

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It has also been shown that in cholesterol fed rabbit, an animal model of diet induced atherosclerosis, arachidonic acid metabolism is an important factor in early lesion development. In particular a shift in metabolism from TxA₂ to PGE₂ may suppress lesion development (i.e. atheromatous plaque) in hypercholesterolemia.

The compounds of invention can be therefore used in this pathology.

The compounds of the invention can also be used in association with thrombolytic agents (e.g. tPA, Streptokinase, pro-Urokinase) in order to reduce the dose of the latter required in thrombolytic therapy, and to lower the incidence of reocclusion and possibly haemorrhage.

A further application of the compounds of the invention is the prevention and/or treatment of restenosis after percutaneous transluminal angioplasty.

The toxicity of the compounds of the invention is negligible, therefore they can be safely used in therapy. Mice and rats which had been deprived of food for nine hours were treated orally with single administrations of increasing doses of compounds of the invention, then housed and normally fed. The orientative acute toxicity (LD₅₀) was assessed on the seventh day after the treatment.

In view of their high activity and low toxicity, the compounds of the invention can be safely used in medicine. The therapeutic regimen for the different clinical syndromes must be adapted to the type of pathology, taking into account, as usual, also the route of administration,

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the form in which the compound is administered and the age, weight and conditions of the subject involved.

The oral route is employed, in general, for all conditions requiring such compounds. Preference is given to
5 intravenous injection or infusion for the treatment of acute pathological states.

For maintenance regimens the oral or parenteral, e.g. intramuscular, route is preferred.

The dosage level suitable for oral administration to
10 adult humans of the compounds of the invention e.g. (E)(+)-5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoic acid may range from about 50 mg to about 500 mg per dose, 1 to 3 times a day.

Of course, these dosage regimens may be adjusted to provide the optimal therapeutic response.
15

The nature of the pharmaceutical compositions containing the compounds of this invention in association with pharmaceutically acceptable carriers or diluents will, of course, depend upon the desired route of administration.

20 The compositions may be formulated in the conventional manner with the usual ingredients. For example, the compounds of the invention may be administered in the form of aqueous or oily solutions, or suspensions tablets, pills, gelatine capsules, syrups, drops or suppositories.

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Thus, for oral administration, the pharmaceutical compositions containing the compounds of this invention are preferably tablets, pills or gelatine capsules which contain the active substance together with diluents, such as

5 lactose, dextrose, sucrose, mannitol, sorbitol, cellulose; lubricants, for instance silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; or they may also contain binders, such as starches, gelatine, methylcellulose, carboxymethylcellulose, gum-

10 arabic, tragacanth, polyvinylpyrrolidone; disaggregating agents, such as starches, alginic acid, alginates, sodium starch glycolate; effervescent mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and in general, non-toxic and

15 pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example by means of mixing, granulating, tableting, sugar-coating, or film-coating processes. The liquid dispersions for oral

20 administration may be e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol. The suspensions and the emulsions may

25 contain as carrier, for example, a natural gum, agar, sodium

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alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspensions or solutions for intramuscular injections may contain together with the active compound a
5 pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injection or infusion may contain as carrier, for example, sterile water or preferably
10 they may be in the form of sterile aqueous isotonic saline solutions.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier e.g. cocoa-butter, polyethylene glycol, a polyoxyethylene
15 sorbitan fatty acid ester surfactant or lecithin. The following examples illustrate but do not limit the present invention.

Example 1

- To a stirred mixture of 5 g (0.025 moles) of (Z)-1-phenyl-2-(imidazol-1-yl)ethanone oxime and 20 ml of dimethylformamide, 0.9 g (0.03 moles) of sodium hydride dispersion 80 %
- 5 are added portionwise at room temperature. Upon completion, stirring is continued till hydrogen evolution stops.
- Then 4.74 ml (0.03 moles) of ethyl 5-bromopentanoate are added dropwise at room temperature and stirring is continued for 6 hours. The reaction mixture is evaporated under vacuum,
- 10 diluted with water and extracted with chloroform. The organic phase dried over CaCl_2 is evaporated to dryness. The residue is purified by column chromatography over silica gel (eluant: chloroform / methanol = 97/3). The pure fractions are collected and evaporated, yielding 4.41 g (53 %) of ethyl
- 15 (Z)-5-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoate. NMR (CDCl_3):
- | | |
|-----------|---|
| 1.15 | (3H, t, $-\text{COOCH}_2\text{CH}_3$) |
| 1.6-1.9 | (4H, m, $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$) |
| 2.35 | (2H, m, $-\text{CH}_2\text{COO}-$) |
| 20 4.13 | (2H, q, $-\text{COOCH}_2\text{CH}_3$) |
| 4.27 | (2H, m, $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$) |
| 5.16 | (2H, s, $-\text{CH}_2-\text{N}=\text{}$) |
| 6.89 | (1H, dd, CH at 5 position of imidazole ring) |
| 25 6.98 | (1H, dd, CH at 4 position of imidazole ring) |
| 7.25-7.70 | (6H, m, $-\text{N}=\text{CH}-\text{N}-$ + phenyl ring) |

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starting from

By the same procedure, either an (E) or (Z) oxime of formula (II) or a mixture thereof, the following compounds can be prepared:

ethyl (Z)-4-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxylbutanoate:

5 Microanalysis:

Found: C 64.03; H 6.80; N 13.01

Calculated for $C_{17}H_{21}N_3O_3$: C 64.74; H 6.71; N 13.32

NMR ($CDCl_3$):

	1.24	(3H, t, $-COOCH_2CH_3$)
10	2.07	(2H, m, $-OCH_2CH_2CH_2-$)
	2.40	(2H, t, $-OCH_2CH_2CH_2COO-$)
	4.12	(2H, q, $-COOCH_2CH_3$)
	4.30	(2H, t, $-OCH_2CH_2CH_2-$)
	5.15	(2H, s, $-CH_2-N=$)
15	6.88	(1H, bs, \underline{CH} at 5 position of imidazole ring)
	6.98	(1H, bs, \underline{CH} at 4 position of imidazole ring)
	7.30-7.60	(6H, m, $-N=CH-N-$ + phenyl ring)

20 methyl (Z)-3-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxylpropanoate:

Microanalysis:

Found: C 61.81; H 6.05; N 14.35

Calculated for $C_{15}H_{17}N_3O_3$: C 62.71; H 5.96; N 14.62

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NMR (CDCl₃):

	2.80	(2H, t, -CH ₂ COOCH ₃)
	3.70	(3H, s, -COOCH ₃)
	4.54	(2H, t, -OCH ₂ CH ₂ -)
5	5.14	(2H, s, -CH ₂ -N=)
	6.88	(1H, t, CH at 5 position of imidazole ring)
	6.98	(1H, t, CH at 4 position of imidazole ring)
10	7.30-7.60	(6H, m, -N=CH-N- + phenyl ring)

ethyl (Z)-5-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl) ethylidene] aminoxypentanoate:

NMR (CDCl₃):

	1.26	(3H, t, -COOCH ₂ CH ₃)
15	1.6-1.9	(4H, m, -OCH ₂ CH ₂ CH ₂ CH ₂ -)
	2.38	(2H, m, -CH ₂ COO-)
	4.15	(2H, q, -COOCH ₂ CH ₃)
	4.34	(2H, m, -OCH ₂ CH ₂ CH ₂ CH ₂ -)
	5.24	(2H, s, -CH ₂ -N=)
20	6.91	(1H, bs, CH at 5 position of imidazole ring)
	7.04	(1H, bs, CH at 4 position of imidazole ring)
	7.40-7.80	(4H, m, phenyl ring)
25	7.87	(1H, bs, -N=CH-N-)

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ethyl (Z)-5- $\overline{\text{1}}$ -(3-n-butyloxyphenyl)-2-(imidazol-1-yl)
ethylidene $\overline{\text{7}}$ aminoxypentanoate:

Microanalysis:

Found: C 65.32; H 7.86; N 9.93

5 Calculated for $\text{C}_{22}\text{H}_{31}\text{N}_3\text{O}_4$: C 65.81; H 7.78; N 10.47

NMR (CDCl_3):

	0.95	(3H, t, $\underline{\text{CH}}_3\text{-CH}_2\text{-CH}_2\text{-}$)
	1.23	(3H, t, $\text{-COO-CH}_2\text{-}\underline{\text{CH}}_3$)
	1.4-1.8	(8H, m, $\text{-O-CH}_2\text{-}\underline{\text{CH}}_2\text{-}\underline{\text{CH}}_2\text{-CH}_2\text{-COO-+}$ $\text{CH}_3\text{-}\underline{\text{CH}}_2\text{-}\underline{\text{CH}}_2\text{-CH}_2\text{-O-}$)
10	2.34	(2H, m, $\text{-}\underline{\text{CH}}_2\text{-COO-}$)
	3.8-4.3	(6H, m, $\text{-COO-}\underline{\text{CH}}_2\text{-CH}_3\text{+}\text{-O}\underline{\text{CH}}_2\text{-CH}_2\text{-}$ $\text{CH}_2\text{-CH}_3\text{+}\text{-O}\underline{\text{CH}}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-COO-}$)
	5.12	(2H, s, $\text{-}\underline{\text{CH}}_2\text{-N=}$)
15	6.8-7.5	(7H, m, phenyl ring + imidazole ring)

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ethyl (Z)-5-1-(3-pyridyl)-2-(imidazol-1-yl)ethylidene7
aminoxypentanoate:

Microanalysis:

Found: C 60.18; H 6.84; N 16.64

5 Calculated for $C_{17}H_{22}N_4O_3$: C 61.80; H 6.71; N 16.96

NMR ($CDCl_3$):

	1.22	(3H, t, $-COOCH_2-\underline{CH}_3$)
	1.75	(4H, m, $-OCH_2-\underline{CH}_2-\underline{CH}_2-CH_2-$)
	2.35	(2H, m, $-\underline{CH}_2-COO-$)
10	4.10	(2H, q, $-COO\underline{CH}_2-CH_3$)
	4.29	(2H, m, $-O\underline{CH}_2-CH_2-CH_2-CH_2-$)
	5.17	(2H, s, $-\underline{CH}_2-N=$)
	6.8-7.8	(5H, m, <u>CH</u> at 4 and 5 positions of pyridine ring + imidazole ring)
15	8.57	(1H, dd, <u>CH</u> at 6 position of pyridine ring)
	8.78	(1H, dd, <u>CH</u> at 2 position of pyridine ring)

and analogously:

ethyl (Z)-3-oxa-5-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoate;

tert-butyl(±)(E)-5-[1-phenyl-2-(imidazol-1-yl)-2-methylethylidene]aminoxypentanoate;

ethyl (E)-5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoate; and

tert-butyl (E)-5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoate.

10 Example 2

By proceeding according to the method described in Example 1 and starting from the appropriate oxime of formula (II) as a mixture of Z- and E-isomers, after separation by column chromatography over silica gel of the crude reaction mixture, using as eluant chloroform and methanol in different ratios, the following compounds can be obtained either as (Z) or (E) isomer:

tert-butyl(±)(E)-5-[1-phenyl-2-(imidazol-1-yl)-2-methylethylidene]aminoxypentanoate:

20 NMR (CDCl₃):

1.42	(9H, s, -C(CH ₃) ₃)
1.60	(4H, m, -OCH ₂ CH ₂ CH ₂ CH ₂ -)
1.68	(3H, d, -CH(CH ₃)N-)
2.19	(2H, t, -CH ₂ COO-)
25 4.07	(2H, t, -OCH ₂ CH ₂ CH ₂ CH ₂ -)

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	5.12	(1H, q, $-\underline{\text{CH}}(\text{CH}_3)\text{N}-$)
	6.80-7.20	(7H, m, $\underline{\text{CH}}$ at 4 and 5 positions of imidazole ring + phenyl ring)
	7.42	(1H, bs, $-\text{N}=\underline{\text{CH}}-\text{N}-$)
5	tert-butyl(+)(Z)-5-[1-phenyl-2-(imidazol-1-yl)-2-methylethylidene]aminoxypentanoate:	
	NMR (CDCl_3):	
	1.44	(9H, s, $-\text{C}(\underline{\text{CH}}_3)_3$)
	1.60	(4H, m, $-\text{OCH}_2\underline{\text{CH}}_2\underline{\text{CH}}_2\underline{\text{CH}}_2-$)
10	1.73	(3H, d, $-\text{CH}(\underline{\text{CH}}_3)\text{N}-$)
	2.28	(2H, t, $-\underline{\text{CH}}_2\text{COO}-$)
	4.23	(2H, t, $-\text{OCH}_2\underline{\text{CH}}_2\underline{\text{CH}}_2\underline{\text{CH}}_2-$)
	5.97	(1H, q, $-\underline{\text{CH}}(\text{CH}_3)\text{N}-$)
	6.80-7.20	(7H, m, $\underline{\text{CH}}$ at 4 and 5 positions of imidazole ring + phenyl ring)
15	7.52	(1H, bs, $-\text{N}=\underline{\text{CH}}-\text{N}-$)
	ethyl (E)-5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoate:	
	NMR (CDCl_3):	
20	1 - 1.7	(18H, m, protons of cyclohexyl ring + $-\text{CO}-\text{O}-\underline{\text{CH}}_2\underline{\text{CH}}_3 +$ $-\text{O}-\underline{\text{CH}}_2-\underline{\text{CH}}_2\underline{\text{CH}}_2-\text{CH}_2-$)
	2.3	(2H, m, $-\underline{\text{CH}}_2-\text{CO}_2\underline{\text{CH}}_2\underline{\text{CH}}_3$)
	4.1	(4H, m, $-\text{O}-\underline{\text{CH}}_2-\text{CH}_2-\text{CH}_2- +$ $-\text{CO}-\text{O}-\underline{\text{CH}}_2-\text{CH}_3$)
25	4.58	(2H, s, $-\underline{\text{CH}}_2\text{N}=$)
	6.9	(1H, bs, $\underline{\text{CH}}$ at 5 position of imidazole ring)

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7.1 (1H, bs, CH at 4 position of imi-
dazole ring)

7.6 (1H, bs, -N=CH-N)

ethyl (Z)-5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]aminoxy-
5 pentanoate:

Microanalysis:

Found: C 63.25; H 8.74; N 12.17

Calculated for $C_{18}H_{29}N_3O_3$: C 64.45; H 8.71; N 12.53

NMR ($CDCl_3$):

10	1.24	(3H, t, -CO-O-CH ₂ - <u>CH</u> ₃)
	1.0-1.4	(6H, m, <u>CH</u> ₂ at 3, 4, 5 positions of cyclohexyl ring)
	1.5-1.8	(8H, m, <u>CH</u> ₂ at 2, 6 positions of cyclohexyl ring + -O-CH ₂ - <u>CH</u> ₂ - <u>CH</u> ₂ -CH ₂ -)
15	2.0	(1H, m, <u>CH</u> at 1 position of cyclo- hexyl ring)
	2.32	(2H, m, - <u>CH</u> ₂ -CO ₂ CH ₂ CH ₃)
	4.12	(4H, m, -O- <u>CH</u> ₂ -CH ₂ CH ₂ - + -CO-O- <u>CH</u> ₂ CH ₃)
20	4.74	(2H, s, - <u>CH</u> ₂ -N=)
	6.90	(1H, bs, <u>CH</u> at 5 position of imi- dazole ring)
	7.05	(1H, bs, <u>CH</u> at 4 position of imi- dazole ring)
25	7.54	(1H, bs, -N= <u>CH</u> -N-)

MS

335

M^+

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tert-butyl (E)-5-[1-cyclohexyl-2-(imidazol-1-yl)-ethylidene]
aminoxypentanoate:

NMR (CDCl₃):

5	1.15	(6H, m, -CH ₂ at 3, 4, 5 positions of cyclohexyl)
	1.45	(9H, s, -C(CH ₃) ₃)
	1.7	(9H, m, CH at 1 position of cyclohexyl ring + CH ₂ at 2, 6 positions of cyclohexyl ring + -O-CH ₂ -CH ₂ -CH ₂ -CH ₂ -)
10	2.25	(2H, m, -CH ₂ -CO ₂ -C(CH ₃) ₃)
	4.05	(2H, m, -O-CH ₂ -CH ₂ -CH ₂ -)
	4.55	(2H, s, -CH ₂ -N=)
	6.9	(1H, bs, CH at 5 position of imidazole ring)
15	7.05	(1H, bs, CH at 4 position of imidazole ring)
	7.5	(1H, bs, -N=CH-N)

tert-butyl (Z)-5-[1-cyclohexyl-2-(imidazol-1-yl)-ethylidene]
aminoxypentanoate:

20 NMR (CDCl₃):

20	1.2	(6H, m, -CH ₂ at 3, 4, 5 positions of cyclohexyl ring)
	1.4	(9H, s, -C(CH ₃) ₃)
	1.7	(9H, m, CH at 1 position of cyclohexyl ring + CH ₂ at 2, 6 positions of cyclohexyl ring + -O-CH ₂ -CH ₂ -CH ₂ -CH ₂ -)
25		

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	2.25	(2H, m, $-\underline{\text{CH}}_2-\text{CO}_2-\text{C}(\text{CH}_3)_3$)
	4.1	(2H, m, $-\text{O}-\underline{\text{CH}}_2-\text{CH}_2-\text{CH}_2-$)
	4.74	(2H, s, $-\underline{\text{CH}}_2-\text{N}=$)
5	6.9	(1H, bs, $\underline{\text{CH}}$ at 5 position of imidazole ring)
	7.05	(1H, bs, $\underline{\text{CH}}$ at 4 position of imidazole ring)
	7.5	(1H, bs, $-\text{N}=\underline{\text{CH}}-\text{N}$)
10	ethyl (Z)-4-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]aminoxyl butanoate:	
	NMR (CDCl_3):	
	1.24	(3H, t, $-\text{CO}-\text{O}-\text{CH}_2 \underline{\text{CH}}_3$)
	1.1-1.4	(6H, m, $\underline{\text{CH}}_2$ at 3, 4, 5 positions of cyclohexyl ring)
15	1.55-1.8	(4H, m, $\underline{\text{CH}}_2$ at 2, 6 positions of cyclohexyl ring)
	1.95	(1H, m, $\underline{\text{CH}}$ at 1 position of cyclohexyl ring)
	2.1	(2H, m, $-\underline{\text{CH}}_2-\text{CH}_2-\text{CO}-$)
	2.4	(2H, m, $-\text{CH}_2-\underline{\text{CH}}_2-\text{CO}-$)
20	4.15	(4H, m, $-\text{O}-\underline{\text{CH}}_2-\text{CH}_2-\text{CH}_2- + -\text{CO}-\text{O}-\underline{\text{CH}}_2\text{CH}_3$)
	4.75	(2H, s, $-\underline{\text{CH}}_2-\text{N}=$)
	6.90	(1H, bs, $\underline{\text{CH}}$ at 5 position of imidazole ring)
	7.05	(1H, bs, $\underline{\text{CH}}$ at 4 position of imidazole ring)
25	7.48	(1H, bs, $-\text{N}=\underline{\text{CH}}-\text{N}-$)

Example 3

5 To a stirred solution of 3.8 g (0.015 moles) of ethyl (Z)-
5-[1-phenyl-2-(imidazol-1-yl)-ethylidene]aminoxypentanoate
in 20 ml of ethanol, 35 ml of aqueous sodium hydroxyde 1N
are added at room temperature. Stirring is continued for 2
hours, and ethanol is removed under vacuum
10 without heating. The aqueous solution is acidified with acetic
acid till pH 6 with external cooling. The precipitated pro-
duct is filtered, washed with ether and filtered again, yield-
ing 2.63 g (75 %) of (Z)-5-[1-phenyl-2-(imidazol-1-yl)-ethyl-
idene]aminoxypentanoic acid.

15 m.p. 89-90°C

Microanalysis:

Found: C 63.14; H 6.35; N 13.74

Calculated for $C_{16}H_{19}N_3O_3$: C 63.77; H 6.35; N 13.94

NMR (DMSO):

20 1.4-1.8	(4H, m, $-OCH_2CH_2CH_2CH_2-$)
2.25	(2H, m, $-CH_2COOH$)
4.23	(2H, m, $-OCH_2CH_2CH_2CH_2-$)

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5.30	(2H, s, $-\underline{\text{CH}}_2-\text{N}=\text{}$)
6.80	(1H, bs, $\underline{\text{CH}}$ at 5 position of imidazole ring)
7.00	(1H, bs, $\underline{\text{CH}}$ at 4 position of imidazole ring)
7.2-7.7	(6H, m, $-\text{N}=\underline{\text{CH}}-\text{N}-$ + phenyl ring)

By the same procedures the following compounds can be prepared:

(Z)-4-[1-phenyl-2-(imidazol-1-yl)-ethylidene]aminoxybutanoic acid:

10 m.p. 108-109°C

Microanalysis:

Found: C 62.23; H 5.98; N 14.42

Calculated for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3$: C 62.71; H 5.96; N 14.62

NMR (CDCl_3):

15	2.11	(2H, m, $-\text{OCH}_2\underline{\text{CH}}_2\text{CH}_2-$)
	2.41	(2H, t, $-\underline{\text{CH}}_2\text{COOH}$)
	4.34	(2H, t, $-\text{OCH}_2\underline{\text{CH}}_2\text{CH}_2-$)
	5.11	(2H, s, $-\underline{\text{CH}}_2-\text{N}=\text{}$)
20	6.83	(1H, bs, $\underline{\text{CH}}$ at 5 position of imidazole ring)
	6.96	(1H, bs, $\underline{\text{CH}}$ at 4 position of imidazole ring)
	7.30-7.55	(5H, m, phenyl ring)
	7.65	(1H, bs, $-\text{N}=\underline{\text{CH}}-\text{N}-$)
25	10.50	(1H, bs, $-\text{COOH}$)

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(Z)-3-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxymethylbenzoic acid

m.p. 140-142°C

Microanalysis:

5 Found: C 66.51; H 5.10; N 12.00

Calculated for $C_{19}H_{17}N_3O_3$: C 68.04; H 5.10; N 12.52

NMR (DMSO):

5.38 (4H, s, $-\underline{CH}_2-N= + -O\underline{CH}_2-$)

6.78 (1H, dd, \underline{CH} at 5 position of imidazole ring)

10 6.97 (1H, dd, \underline{CH} at 4 position of imidazole ring)

7.25-8.10 (10H, m, $-N=\underline{CH}-N$ + phenyl rings)

15 (Z)-5-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)-ethylidene]aminoxypentanoic acid:

m.p. 124-6°C

Microanalysis:

Found: C 55.24; H 4.92; N 11.20

Calculated for $C_{17}H_{18}F_3N_3O_3$: C 55.28; H 4.91; N 11.38

20 NMR ($CDCl_3$):

1.6-1.9 (4H, m, $-OCH_2\underline{CH}_2\underline{CH}_2CH_2-$)

2.37 (2H, m, $-\underline{CH}_2COO-$)

4.32 (2H, m, $-\underline{OCH}_2CH_2CH_2CH_2-$)

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	6.87	(1H, s, <u>CH</u> at 5 position of imidazole ring)
	7.02	(1H, s, <u>CH</u> at 4 position of imidazole ring)
5	7.40-7.75	(4H, m, phenyl ring)
	7.86	(1H, s, -N= <u>CH</u> -N-)

(Z)-5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid:

m.p. 80-82°C

10 Microanalysis:

Found: C 62.26; H 7.85; N 13.46

Calculated for $C_{16}H_{25}N_3O_3$: C 62.5; H 8.2; N 13.67

NMR ($CDCl_3$):

15	1.0-1.4	(6H, m, <u>CH₂</u> of 3, 4, 5 positions of cyclohexyl ring)
	1.55-1.85	(8H, m, <u>CH₂</u> of 2, 6 positions of cyclohexyl ring + -O- <u>CH₂</u> - <u>CH₂</u> - <u>CH₂</u> -CH ₂ -)
	2.05	(1H, m, <u>CH</u> at 1 position of cyclohexyl ring)
	2.35	(2H, m, - <u>CH₂</u> -COOH)
20	4.10	(2H, m, -O- <u>CH₂</u> -CH ₂ -CH ₂ -)
	4.72	(2H, s, - <u>CH₂</u> -N=)
	6.91	(1H, bs, <u>CH</u> at 5 position of imidazole ring)
	7.05	(1H, bs, <u>CH</u> at 4 position of imidazole ring)
	7.66	(1H, bs, -N= <u>CH</u> -N-)

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(E)-5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]aminoxy-pentanoic acid:

m.p. 117-119°C

Microanalysis:

5 Found: C 62.14; H 13.34; N 8.01

Calculated for $C_{16}H_{25}N_3O_3$: C 62.5; H 8.2; N 13.67

NMR ($CDCl_3$):

	1.0-1.4	(6H, m, \underline{CH}_2 at 3, 4, 5 positions of cyclohexyl ring)
10	1.5-1.8	(8H, m, \underline{CH}_2 at 2,6 positions of cyclohexyl ring + $-O-CH_2-\underline{CH}_2-\underline{CH}_2-CH_2-$)
	2.40	(2H, m, $-\underline{CH}_2-COOH$)
	2.97	(1H, m, \underline{CH} at 1 position of cyclohexyl ring)
	4.08	(2H, m, $-O-\underline{CH}_2-CH_2-CH_2-$)
15	4.56	(2H, s, $-\underline{CH}_2-N=$)
	6.94	(1H, bs, \underline{CH} at 5 position of imidazole ring)
	7.07	(1H, bs, \underline{CH} at 4 position of imidazole ring)
	7.68	(1H, bs, $-N=\underline{CH}-N-$)

20 (Z) -4-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]aminoxybutanoic acid:

m.p. 120-122°C

Microanalysis:

Found: C 60.74; H 8.28; N 13.83

Calculated for: $C_{15}H_{23}N_3O_3$: C 61.41; H 7.90; N 14.3

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NMR (CDCl_3):

1.1-1.4	(6H, m, CH_2 at 3, 4, 5 positions of cyclohexyl ring)
1.6-1.8	(4H, m, CH_2 at 2, 6 positions of cyclohexyl ring)
1.95-2.15	(3H, m, CH at 1 position of cyclohexyl ring + $-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-$)
2.39	(2H, t, $-\text{CH}_2-\text{COOH}$)
4.17	(2H, t, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-$)
4.65	(2H, s, $-\text{CH}_2-\text{N}=\text{}$)
6.85	(1H, bs, CH at 5 position of imidazole ring)
7.02	(1H, bs, CH at 4 position of imidazole ring)
7.50	(1H, bs, $-\text{N}=\text{CH}-\text{N}-$)

(Z)-6-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxihexanoic acid:

m.p. 109-110°C

Microanalysis:

Found: C 64.42; H 6.72; N 13.10

Calculated for $\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_3$: C 64.74; H 6.71; N 13.31

NMR (DMSO):

1.3-1.8	(6H, m, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$)
2.22	(2H, t, $-\text{CH}_2-\text{COO}-$)
4.22	(2H, t, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-$)
5.30	(2H, s, $-\text{CH}_2-\text{N}=\text{}$)
6.8-7.7	(8H, m, phenyl ring + imidazole ring)

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and analogously:

- (Z)-5-[1-(3-bromophenyl)-2-(imidazol-1-yl)ethylidene]aminoxy-pentanoic acid;
- (Z)-4-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)ethylidene]aminoxybutanoic acid;
- (Z)-5-[1-(3-(n-butyl)phenyl)-2-(imidazol-1-yl)ethylidene]aminoxy-pentanoic acid;
- (Z)-5-[1-(2-methoxyphenyl)-2-(imidazol-1-yl)ethylidene]aminoxy-pentanoic acid;
- (Z)-3-oxa-5-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- (Z)-3-oxa-5-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
- (Z)-5-[1-(3-n-butyloxyphenyl)-2-(imidazol-1-yl)ethylidene]aminoxy-pentanoic acid;
- m.p. 104-105°C
- Microanalysis:
- Found: C 64.28; H 7.28; N 11.10
- Calculated for $C_{20}H_{27}N_3O_4$: C 64.32; H 7.24; N 11.25
- NMR ($CDCl_3$):
- | | |
|----------|--|
| 0.95 | (3H, t, $\underline{CH}_3-CH_2-CH_2-$ |
| 1.35-1.9 | (8H, m, $\underline{CH}_3-\underline{CH}_2-\underline{CH}_2-CH_2-O-$ +
-O- $\underline{CH}_2-\underline{CH}_2-\underline{CH}_2-CH_2-COO-$) |
| 2.35 | (2H, m, $-\underline{CH}_2-COO-$) |
| 3.93 | (2H, t, $-O-\underline{CH}_2-CH_2-CH_2-CH_3$) |

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4.25 (2H, m, -O-CH₂-CH₂-CH₂-CH₂-COO-)
5.13 (2H, s, -CH₂-N=)
6.75-7.7 (7H, m, phenyl ring + imidazole ring)

5 (Z)-5-1-(3-pyridyl)-2-(imidazol-1-yl)ethylideneaminoxy-
pentanoic acid:

m.p. 65-70°C

Microanalysis:

Found: C 58.90; H 6.01; N 17.93

Calculated for C₁₅H₁₈N₄O₃ : C 59.59; H 6.00; N 18.53

10 NMR (CDCl₃):

1.6-1.9 (4H, m, -O-CH₂-CH₂-CH₂-CH₂-)
2.35 (2H, m, -CH₂-COO-)
4.30 (2H, m, -OCH₂-CH₂-CH₂-CH₂-)
5.20 (2H, s, -CH₂-N=)
15 6.85-7.90 (5H, m, CH at 4 and 5 positions of
pyridine ring + imidazole ring)
8.58 (1H, dd, CH at 6 position of
pyridine ring)
8.81 (1H, d, CH at 2 position of
20 pyridine ring)

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(Z)-4-1-(3-pyridyl)-2-(imidazol-1-yl)ethylidene7aminoxy-
butanoic acid:

Microanalysis:

Found: C 57.41; H 5.54; N 18.92

5 Calculated for $C_{14}H_{16}N_4O_3$: C 61.30; H 5.82; N 20.43NMR ($CDCl_3$):

	2.11	(2H, m, $-O-CH_2-\underline{CH}_2-CH_2-COO-$)
	2.43	(2H, m, $-\underline{CH}_2-COO-$)
	4.37	(2H, m, $-O-\underline{CH}_2-CH_2-CH_2-$)
10	5.13	(2H, s, $-\underline{CH}_2-N=$)
	6.8-7.8	(5H, m, <u>CH</u> at 4 and 5 positions of pyridine ring + imidazole ring)
	8.55	(1H, dd, <u>CH</u> at 6 position of pyridine ring)
15	8.76	(1H, d, <u>CH</u> at 2 position of pyridine ring)

(E)-4-1-cyclohexyl-2-(imidazol-1-yl)ethylidene7aminoxy-
butanoic acid:

m.p. 126-129°C

Microanalysis

20 Found: C 61.22; H 7.73; N 13.93

Calculated for $C_{15}H_{23}N_3O_3$: C 61.41; H 7.90; N 14.3NMR ($CDCl_3$)

	0.9-1.75	(10H, m, <u>CH</u> ₂ at 2, 3, 4, 5, 6 position of cyclohexyl ring)
25	2.0	(2H, m, $-O-CH_2-\underline{CH}_2-CH_2-$)

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	2.40	(2H, m, $-\underline{\text{CH}}_2-\text{COOH}$)
	2.95	(1H, m, $\underline{\text{CH}}$ at 1 position of cyclohexyl ring)
	4.10	(2H, m, $-\text{O}-\underline{\text{CH}}_2-\text{CH}_2-\text{CH}_2-$)
5	4.55	(2H, s, $-\underline{\text{CH}}_2-\text{N}=\text{)$
	6.93	(1H, bs, $\underline{\text{CH}}$ at 5 position of imidazole ring)
	7.06	(1H, bs, $\underline{\text{CH}}$ at 4 position of imidazole ring)
10	7.68	(1H, bs, $-\text{N}=\underline{\text{CH}}-\text{N}-$)
(Z)-6- <u>1</u> -cyclohexyl-2-(imidazol-1-yl)ethylidene <u>7</u> aminoxy-hexanoic acid:		
m.p. 107-108°C		
Microanalysis:		
15	Found: C 63.08; H 8.57; N 8.01	
Calculated for $\text{C}_{17}\text{H}_{27}\text{N}_3\text{O}_3$: C 63.53; H 8.47; N 13.07		
NMR (CDCl_3)		
	1.1-1.85	(16H, m, $\underline{\text{CH}}_2$ at 2,3,4,5,6 position of cyclohexyl ring + $-\text{O}-\underline{\text{CH}}_2-\underline{\text{CH}}_2-\underline{\text{CH}}_2-\underline{\text{CH}}_2-$)
20	2.05	(1H, m, $\underline{\text{CH}}$ at 1 position of cyclohexyl ring)
	2.33	(2H, m, $-\underline{\text{CH}}_2-\text{COOH}$)
	4.07	(2H, m, $-\text{O}-\underline{\text{CH}}_2-\text{CH}_2-\text{CH}_2-$)
	4.69	(2H, s, $-\underline{\text{CH}}_2-\text{N}=\text{)$
25	6.88	(1H, bs, $\underline{\text{CH}}$ at 5 position of imidazole ring)

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7.02 (1H, bs, CH at 4 position of imidazole ring)

7.63 (1H, bs, -N=CH-N-)

5 (E)-5-1-n-hexyl-2-(imidazol-1-yl)ethylideneaminoxy-pentanoic acid:

m.p. 82-85°C

Microanalysis:

Found: C 61.81; H 8.54; N 13.28

Calculated for $C_{16}H_{27}N_3O_3$: C 62.11; H 8.79; N 13.58

10 NMR ($CDCl_3$):

0.87 (3H, m, CH₃-CH₂-CH₂-)

1.05-1.58 (8H, m, CH₃-(CH₂)₄-)

1.58-1.94 (4H, m, -O-CH₂-CH₂-CH₂-CH₂-)

1.94-2.60 (4H, m, -CH₂-COO-+-CH₂-CH₂-C=N-)

15 4.11 (2H, m, -O-CH₂-CH₂-CH₂-CH₂)

4.57 (2H, s, -CH₂-N=)

6.94 (1H, bs, CH at 5 position of imidazole ring)

7.09 (1H, bs, CH at 4 position of imidazole ring)

20

7.66 (1H, bs, -N=CH-N-)

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(Z)-5-1-n-hexyl-2-(imidazol-1-yl)ethylideneaminoxy-
pentanoic acid:

Microanalysis:

Found: C 61.94; H 8.79; N 13.36

5 Calculated for $C_{16}H_{27}N_3O_3$: C 62.11; H 8.79; N 13.58

NMR ($CDCl_3$):

	0.87	(3H, m, $\underline{CH}_3-CH_2-CH_2$)
	1.02-1.60	(8H, m, $CH_3-(\underline{CH}_2)_4-$)
	1.60-1.88	(4H, m, $-O-CH_2-\underline{CH}_2-\underline{CH}_2-CH_2-$)
10	1.88-2.24	(2H, m, $-CH_2-\underline{CH}_2-C=N-$)
	2.39	(2H, m, $-\underline{CH}_2-COO-$)
	4.14	(2H, m, $-O-\underline{CH}_2-CH_2-CH_2-CH_2-$)
	4.81	(2H, s, $-\underline{CH}_2-N=$)
15	6.92	(1H, bs, \underline{CH} at 5 position of imidazole ring)
	7.10	(1H, bs, \underline{CH} at 4 position of imidazole ring)
	7.65	(1H, bs, $-N=\underline{CH}-N-$)

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4-[1-phenyl-3-(imidazol-1-yl)propylidene]aminoxypentanoic acid;
3-oxa-5-/1-cyclohexyl-2-(imidazol-1-yl)ethylidene/aminoxypentanoic acid;

5-/1-(3,3-dimethylcyclohexyl)-2-(imidazol-1-yl)ethylidene/aminoxypentanoic acid;

5 5-/1-cyclopentyl-2-(imidazol-1-yl)ethylidene/aminoxypentanoic acid;

(Z)-5-/1-(2-thienyl)-2-(imidazol-1-yl)ethylidene/aminoxypentanoic acid;

10 3-oxa-6-/1-cyclohexyl-2-(imidazol-1-yl)ethylidene/aminoxihexanoic acid;

5-/1-cycloheptyl-2-(imidazol-1-yl)ethylidene/aminoxypentanoic acid;

6-/1-cycloheptyl-2-(imidazol-1-yl)ethylidene/aminoxihexanoic acid; and

15 5-/1-n-heptyl-2-(imidazol-1-yl)ethylidene/aminoxypentanoic acid.

Example 4

Trifluoroacetic acid (1.3 ml) is added dropwise at -10°C to 0.23 g (0.643 mmoles) of tert-butyl (E)-5-/1-phenyl-2-(imidazol-1-yl)ethylidene/aminoxypentanoate. The mixture is stirred at
20 -10°C for 1 hour and 30 minutes. A cooled saturated sodium hydrogencarbonate solution is added to the reaction mixture at 0°C till pH=7 and the mixture is extracted with ethyl acetate. The aqueous phase is cooled, acidified with acetic acid and extracted twice with ethyl acetate. The organic
25 phase is dried and evaporated. The residue is taken up twice with

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toluene and evaporated under vacuum without heating, yielding 0.11 g (57%) of (E)-5-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid.

Microanalysis:

5 Found: C 59.12; H 5.93; N 12.23

Calculated for $C_{16}H_{19}N_3O_3$: C 63.77; H 6.35; N 13.94

NMR ($CDCl_3$):

	1.75	(4H, m, $-OCH_2CH_2CH_2CH_2-$)
	2.39	(2H, m, $-CH_2COOH$)
10	4.12	(2H, m, $-OCH_2CH_2CH_2CH_2-$)
	4.92	(2H, s, $-CH_2-N=$)
	6.87	(1H, bs, CH at 5 position of imidazole ring)
	7.02	(1H, bs, CH at 4 position of imidazole ring)
	7.2-7.5	(5H, m, phenyl ring)
15	7.72	(1H, bs, $-N=CH-N-$)

By the same procedure the following compounds can be prepared:

(+)(E)-5-[1-phenyl-2-(imidazol-1-yl)-2-methylethylidene]aminoxypentanoic acid:

Microanalysis:

20 Found: C 64.20; H 6.56; N 12.72

Calculated for $C_{17}H_{21}N_3O_3$: C 64.74; H 6.71; N 13.32

NMR($CDCl_3$):

	1.5-1.8	(7H, m, $-CH(CH_3)N--OCH_2CH_2CH_2CH_2$)
	2.35	(2H, m, $-CH_2COO-$)
25	4.10	(2H, m $-OCH_2CH_2CH_2CH_2-$)

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5.24 (1H, q, $-\underline{\text{CH}}(\text{CH}_3)\text{N}-$)
 6.9-7.5 (7H, m, $\underline{\text{CH}}$ at 4 and 5 positions of imidazole ring + phenyl ring)
 8.01 (1H, bs, $-\text{N}=\underline{\text{CH}}-\text{N}-$)

5 (+)(Z)-5-[1-phenyl-2-(imidazol-1-yl)-2-methylethylidene]aminoxypentanoic acid;

NMR(CDCl_3):

1.6-1.9 (7H, m, $-\text{CH}(\underline{\text{CH}}_3)\text{N}- + -\text{OCH}_2\underline{\text{CH}}_2\underline{\text{CH}}_2\underline{\text{CH}}_2-$)
 2.40 (2H, m, $-\underline{\text{CH}}_2\text{COO}-$)
 10 4.25 (2H, m, $-\text{OCH}_2\underline{\text{CH}}_2\underline{\text{CH}}_2\underline{\text{CH}}_2-$)
 5.98 (1H, q, $-\text{CH}(\text{CH}_3)\text{N}-$)
 6.8-7.4 (7H, m, $\underline{\text{CH}}$ at 4 and 5 positions of imidazole ring + phenyl ring)
 7.82 (1H, bs, $-\text{N}=\underline{\text{CH}}-\text{N}-$)

15 and analogously:

(E)-4-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

(E)-5-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

20 (E)-5-[1-(3-bromophenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

(E)-4-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

25 (E)-5-[1-(3-(n-butyl)phenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

(E)-5-[1-(2-methoxyphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

(E)-3-oxa-5-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

(E)-3-oxa-5-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

5 (E)-3-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxymethylbenzoic acid;

(E)-5-[1-(2-thienyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

10 (E)-5-[1-(3-pyridyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid; and

(E)-4-[1-(3-pyridyl)-2-(imidazol-1-yl)ethylidene]aminoxybutanoic acid.

Example 5

15 To a stirred mixture of 0.50 g (0.0025 moles) of (Z)-1-phenyl-2-(imidazol-1-yl)ethanone oxime and 2 ml of dimethylformamide, 0.15 g (0.0034 moles) of sodium hydride dispersion 55% are added portion-wise at room temperature. Upon completion, stirring is continued till hydrogen evolution stops; then 0.42 g (0.0049 moles) of γ -butyrolactone are added and the mixture is heated at 80°C
20 for 4 hours.

The reaction mixture is evaporated under vacuum, diluted with water and acidified with acetic acid till pH 6, with external cooling. The precipitated product is filtered, washed with ether and filtered again, yielding 0.40 g (56%) of (Z)-4-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxybutanoic acid.
25

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m.p. 108-109°C

Microanalysis:

Found: C 62.23; H 5.98; N 14.42

Calculated for $C_{15}H_{17}N_3O_3$: C 62.71; H 5.96; N 14.625 NMR ($CDCl_3$):

2.11	(2H, m, $-OCH_2CH_2CH_2-$)
2.41	(2H, t, $-CH_2COOH$)
4.34	(2H, t, $-OCH_2CH_2CH_2-$)
5.11	(2H, s, $-CH_2-N=$)
10 6.83	(1H, bs, \underline{CH} at 5 position of imidazole ring)
6.96	(1H, bs, \underline{CH} at 4 position of imidazole ring)
7.30-7.55	(5H, m, phenyl ring)
15 7.65	(1H, bs, $-N=\underline{CH}-N-$)
10.50	(1H, bs, $-COOH$)

By proceeding analogously the following compounds can be obtained:

- 20 4-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)ethylidene]aminoxybutanoic acid:
- 4-[1-phenyl-3-(imidazol-1-yl)propylidene]aminoxybutanoic acid:
- 4-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]aminoxybutanoic acid:
- and
- 4-[1-(3-pyridyl)-2-(imidazol-1-yl)ethylidene]aminoxybutanoic acid.

Example 6

To a solution of 400 mg (1.19 mmoles) of ethyl (E)-5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene] aminoxypentanoate in 5 ml of 1,4-dioxane, 9 ml of an aqueous ammonium hydroxide solution 30% are added. After stirring for 48 hours at room temperature the reaction mixture is diluted with water, extracted twice with ethyl acetate, dried and evaporated. The residue is purified by column chromatography over silica gel (eluant: methylene chloride/methanol=95/5). The pure fractions are collected and evaporated, yielding 140 mg (60%) of (E)-5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene] aminoxypentanamide.

NMR (CDCl₃):

	1.0-1.4	(6H, m, <u>CH</u> ₂ at 3, 4, 5 positions of cyclohexyl ring)
15	1.5-1.8	(8H, m, <u>CH</u> ₂ at 2, 6 positions of cyclohexyl ring + -O-CH ₂ - <u>CH</u> ₂ - <u>CH</u> ₂ -CH ₂ -)
	2.25	(2H, m, - <u>CH</u> ₂ CO-)
	2.93	(1H, m, <u>CH</u> at 1 position of cyclohexyl ring)
	4.07	(2H, m, -O- <u>CH</u> ₂ -CH ₂ -CH ₂ -)
20	4.57	(2H, s, -CH ₂ -N=)
	4.70	(1H, bs, CONH ₂)
	5.70	(1H, bs, CONH ₂)
	6.93	(1H, bs, <u>CH</u> at 5 position of imidazole ring)
	7.06	(1H, bs, <u>CH</u> at 4 position of imidazole ring)
25	7.63	(1H, bs, -N= <u>CH</u> -N-)

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By proceeding analogously the following compound can be prepared:

(Z)-5-1-(3-pyridyl)-2-(imidazol-1-yl)ethylidene/aminoxy-pentanamide:

m.p. 102-107°C

5 Microanalysis:

Found: C 58.69; H 6.35; N 21.93

Calculated for $C_{15}H_{19}N_5O_2$: C 59.80; H 6.36; N 23.24

NMR ($CDCl_3$):

	1.6-1.9	(4H, m, -O-CH ₂ -CH ₂ -CH ₂ -CH ₂ -)
10	2.20	(2H, m, -CH ₂ -CONH ₂)
	4.3	(2H, m, -O-CH ₂ -CH ₂ -CH ₂ -CH ₂ -)
	5.17	(2H, s, -CH ₂ -N=)
	5.55	(1H, bs, -CO-NH _A)
	5.90	(1H, bs, -CO-NH _B)
15	6.8-7.9	(5H, m, CH at 4 and 5 positions of pyridine ring + imidazole ring)
	8.59	(1H, dd, CH at 6 position of pyridine ring)
	8.82	(1H, d, CH at 2 position of pyridine ring)
20		

and similarly:

5-1-phenyl-2-(imidazol-1-yl)ethylidene/aminoxypentanamide.

Example 7

To a stirred mixture of 1.5 g (0.005 moles) of (+)(E+Z)-1-phenyl-2-(imidazol-1-yl)-2-benzylethanone oxime and 10 ml of dimethylformamide, 0.26 g (0.006 moles) of sodium hydride dispersion 55 % are added portionwise at room temperature. Upon completion, stirring is continued till hydrogen evolution stops. Then 0.79 ml (0.005 moles) of ethyl 5-bromopentanoate are added at room temperature and stirring is continued for 6 hours. The reaction mixture is diluted with water and extracted twice with ethyl acetate. The organic phase is washed with water and with saturated sodium chloride solution, dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue is purified by column chromatography over silica gel (eluant: dichloromethane/methanol = 190/10) yielding 1.25 g (60 %) of ethyl (+)(E+Z)-5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoate.

Microanalysis:

Found: C 70.31; H 6.92; N 9.54.

Calculated for $\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_3$: C 71.58; H 6.97; N 10.02.20 NMR (CDCl_3):5.07 (1H, dd, $\underline{\text{CH}}\text{-N=}$, E isomer)6.03 (1H, t, $\underline{\text{CH}}\text{-N=}$, Z isomer)

Analogously the following compound can be prepared:

ethyl (+)(E+Z)-5-[1-cyclohexyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoate.

Example 8

To a stirred solution of 1 g (0.0024 moles) of ethyl (+)(E+Z)-5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoate in 20 ml of ethanol, 10 ml of aqueous sodium hydroxide
5 1N are added at room temperature. Stirring is continued for 30' at 60°C and then ethanol is removed under vacuum. The aqueous solution is acidified with acetic acid till pH 6 with external cooling and extracted three times with ethyl acetate. The organic phase is washed with water, with saturated sodium
10 chloride solution, dried over anhydrous Na₂SO₄ and evaporated to dryness. The residue is purified by column chromatography over silica gel (eluant: chloroform/methanol = 180/20) yielding 0.235 g of (+)(E)-5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoic acid and 0.427 g of the corresponding
15 "Z" isomer.
(+)(E)-5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoic acid:

Microanalysis:

Found: C 69.13; H 6.58; N 10.33.

20 Calculated for C₂₃H₂₅N₃O₃: C 70.57; H 6.44; N 10.73.NMR (CDCl₃):

1.7	(4H, m, -O-CH ₂ -CH ₂ -CH ₂ -CH ₂ -COO-)
2.35	(2H, m, -CH ₂ -COO-)
3.25	(1H, dd, Ph-CH _A -)
25 3.49	(1H, dd, Ph-CH _B -)
4.15	(2H, m, -O-CH ₂ -CH ₂ -CH ₂ -CH ₂ -COO-)
5.09	(1H, dd, -CH-N=)
6.8-7.5	(13H, m, 2 phenyl rings + imidazole ring)

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(+)(Z)-5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoic acid:

Microanalysis:

Found: C 68.21; H 6.68; N 9.94.

5 Calculated for $C_{23}H_{25}N_3O_3$: C 70.57; H 6.44; N 10.73.

NMR ($CDCl_3$):

	1.7	(4H, m, -O-CH ₂ -CH ₂ -CH ₂ -CH ₂ -COO-)
	2.35	(2H, m, -CH ₂ -COO-)
	3.35	(1H, dd, Ph-CH _A -)
10	3.49	(1H, dd, Ph-CH _B -)
	4.2	(2H, m, -O-CH ₂ -CH ₂ -CH ₂ -CH ₂ -COO-)
	6.00	(1H, dd, -CH-N=)
	6.8-7.7	(13H, m, 2 phenyl rings + imidazole ring)

15 By the same procedure, starting from either an (E) or (Z) ester, prepared according to the method described in Example 1, or a mixture thereof, the following compounds can be prepared:

(+)(Z)-5-[1-cyclohexyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoic acid:

20 NMR ($CDCl_3$):

	0.53-2.15	(14H, m, -OCH ₂ -CH ₂ -CH ₂ -CH ₂ -COO- + CH ₂ at 2,3,4,5 and 6 positions of cyclohexyl ring)
	2.15-2.60	(3H, m, -CH ₂ COO- + CH at 1 position of cyclohexyl ring)
25	2.76-3.60	(2H, m, Ph-CH ₂ -)

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4.10 (2H,m,-O-CH₂-CH₂)
 5.62 (1H,dd,-CH-N=)
 6.67-7.42 (7H,m,phenyl ring + CH at 4 and 5 positions
 of imidazole ring)

5 7.73 (1H,bs,-N=CH-N-);
 (+)(E)-5-[1-cyclohexyl-2-(imidazol-1-yl)-2-benzylethylidene]
 aminoxypentanoic acid:

NMR (CDCl₃):

10 0.37-2.16 (14H,m,-OCH₂CH₂CH₂-CH₂-COO- +
 CH₂ at 2,3,4,5 and 6 positions of cyclohexyl
 ring)
 2.41 (2H,m,-CH-COO-)
 2.61-3.63 (3H,m,Ph-CH₂ + CH at 1 position of cyclohexyl
 ring)

15 4.19 (2H,m,-O-CH₂-CH₂-)
 4.87 (1H,dd,-CH-N=)
 6.52-7.40 (7H,m,phenyl ring + CH at 4 and 5 positions
 of imidazole ring)

20 7.58 (1H,bs,-N=CH-N-);
 (+)(Z)-6-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]amin-
 oxyhexanoic acid:

Microanalysis:

Found: C 70.11; H 6.83; N 9.99.

Calculated for C₂₄H₂₇N₃O₃: C 71.09; H 6.71; N 10.36.

25 NMR (CDCl₃):

1.3-1.7 (6H,m,-O-CH₂-CH₂-CH₂-CH₂-CH₂-)
 2.35 (2H,m,-CH₂-COO-)
 3.33 (1H,dd,Ph-CH_A-)

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- 3.49 (1H, dd, Ph-CH_B-)
 4.2 (2H, m, -OCH₂CH₂CH₂CH₂CH₂-)
 5.97 (1H, t, -CH-N=)
 6.8-7.8 (13H, m, 2 phenyl rings + imidazole ring);
 5 (+)(E)-6-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene] aminoxyhexanoic acid;

Microanalysis:

Found: C 70.32; H 6.63; N 10.15

Calculated for C₂₄H₂₇N₃O₃: C 71.09; H 6.71; N 10.3610 NMR (CDCl₃):

- 1.2-1.8 (6H, m, -OCH₂-CH₂CH₂-CH₂-CH₂-)
 2.3 (2H, m, -CH₂COO-)
 3.27 (1H, dd, PhCH_A-)
 3.51 (1H, dd, Ph-CH_B-)
 15 4.1 (2H, m, -OCH₂CH₂CH₂CH₂CH₂-)
 5.10 (1H, dd, -CH-N=)
 6.8-7.6 (13H, m, 2 phenyl rings + imidazole ring);

(+)(Z)-6-[1-cyclohexyl-2-(imidazol-1-yl)-2-benzylethylidene] aminoxyhexanoic acid;

20 (+)(E)-6-[1-cyclohexyl-2-(imidazol-1-yl)-2-benzylethylidene] aminoxyhexanoic acid;

(+)(Z)-5-[1-(4-fluorophenyl)-2-(imidazol-1-yl)-2-(4-fluorobenzyl)ethylidene] aminoxypentanoic acid;

25 (+)(E)-5-[1-(4-fluorophenyl)-2-(imidazol-1-yl)-2-(4-fluorobenzyl)ethylidene] aminoxypentanoic acid;

(+)(Z)-5-[1-cyclohexyl-2-(imidazol-1-yl)-2-(4-fluorobenzyl)ethylidene] aminoxypentanoic acid;

(+)(E)-5-[1-cyclohexyl-2-(imidazol-1-yl)-2-(4-fluorobenzyl)ethylidene] aminoxypentanoic acid;

(+)(Z)-3-oxa-5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoic acid; and

(+)(E)-3-oxa-5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]aminoxypentanoic acid.

5 Example 9

To a stirred solution of 1 g (0.005 moles) of (Z)-5-/1-phenyl-2-(imidazol)-1-yl)ethylidene/aminoxypentanoic acid in 10 ml of methanol, 820 mg (0.015 moles) of a sodium methoxide solution in methanol are added. The reaction mixture is evaporated and the precipitate product is filtered off and dried yielding 970 mg (60%) of sodium (Z)-5-/1-phenyl-2-(imidazol-1-yl)ethylidene/aminoxypentanoate.

Example 10

Tablets, each weighing 150 mg and containing 50 mg of the active substance can be manufactured as follows:

Composition (for 10,000 tablets)

(Z)-5-/ <u>1</u> -cyclohexyl-2-(imidazol-1-yl)ethylidene/aminoxypentanoic acid	500 g
Lactose	710 g
20 Corn starch	237.5 g
Talc powder	37.5 g
Magnesium stearate	15 g

(Z)-5-/1-cyclohexyl-2-(imidazol-1-yl)ethylidene/aminoxypentanoic acid, lactose and a half of the corn starch are mixed: the mixture is then forced through a sieve of 0.5 mm openings. Corn starch (18 mg) is suspended in warm water (180 ml). The resulting paste is used to granulate the powder. The granules are dried, comminuted on a sieve of sieve size 1.4 mm, then the remaining quantity of starch, talc and 30 magnesium are added, carefully mixed, and processed into tablets using punches of 8 mm diameter.

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Example 11

Tablets, each weighing 150 mg and containing 50 mg of the active substance can be manufactured as follows:

Composition (for 10,000 tablets)

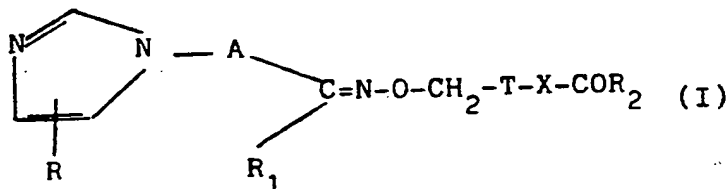
5	+5-(E)-[1-phenyl-2-(imidazol-1-yl)-2-benzyl-ethylidene]aminoxypentanoic acid	500	g
	Lactose	710	g
	Corn starch	237.5	g
	Talc powder	37.5	g
10	Magnesium stearate	15	g

+5-(E)-[1-phenyl-2-(imidazol-1-yl)-2-benzyl-ethylidene]aminoxypentanoic acid, lactose and a half of the corn starch are mixed: the mixture is then forced through a sieve of 0.5 mm openings. Corn starch (18 mg) is suspended in warm water (180 ml). The resulting paste is used to granulate the powder. The granules are dried, comminuted on a sieve of sieve size 1.4 mm, then the remaining quantity of starch, talc and magnesium are added, carefully mixed, and processed into tablets using punches of 8 mm diameter.

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CLAIMS

1. A compound of general formula (I)



wherein

R is hydrogen or C₁-C₄ alkyl;

5 A is a C₁-C₄ alkylene chain unsubstituted or substituted by a phenyl ring unsubstituted or substituted by one or two substituents chosen independently from halogen and trifluoromethyl;

R₁ is a) hydrogen or a straight or branched, saturated or
 10 unsaturated C₁-C₁₀ hydrocarbon radical; b) an aryl or aryl-C₁-C₄ alkyl group, wherein the aryl group or the aryl moiety is unsubstituted or substituted either by one to four substituents independently chosen from halogen, trihalomethyl, C₁-C₄ alkyl, C₂-C₃ alkenyl, C₂-C₆ alkynyl,
 15 C₁-C₄ alkoxy, C₁-C₄ alkylthio and C₁-C₄ alkylsulfonyl or by a substituent chosen from C₅-C₈ alkyl, C₄-C₈ alkenyl, C₅-C₈ alkoxy, C₅-C₈ alkylthio and phenyl, in which the phenyl ring is unsubstituted or substituted by a substituent chosen from halogen, trihalomethyl and C₁-C₄ alkyl; or (c) a C₅-C₈
 20 cycloalkyl or C₅-C₈ cycloalkyl-C₁-C₄ alkyl group, wherein the cycloalkyl group or moiety is unsubstituted or substituted by one to three C₁-C₄ alkyl groups;

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T is a straight or branched, saturated or unsaturated C₁-C₆ hydrocarbon chain, or a phenylene radical;

X is a bond or a divalent group consisting of -O-CH₂-,
-C(R' R'')-, -Si(R' R'')-, vinylene or isopropenylene, wherein
5 each of R' and R'' being the same or different is hydrogen,
fluorine or C₁-C₄ alkyl;

R₂ is an -OR₃ or -N(R₃R₄) group, wherein each of R₃ and R₄
independently is hydrogen, C₁-C₆ alkyl, phenyl or benzyl;
and the pharmaceutically acceptable salts thereof.

10 2. A compound of formula (I), according to claim
1, wherein

R is hydrogen or methyl;

A is a C₁-C₄ alkylene chain optionally substituted by
phenyl, in its turn optionally substituted by one or two
15 substituents independently chosen from halogen and
trifluoromethyl;

R₁ is a) C₁-C₈ alkyl or C₂-C₈ alkenyl; b) a phenyl,
naphthyl, thienyl or pyridyl group unsubstituted or
substituted either by one or two substituents independently
20 chosen from halogen, trihalomethyl, C₁-C₄ alkyl, C₁-C₄
alkoxy, C₁-C₄ alkylsulfonyl and C₁-C₄ alkylthio, or by a
substituent chosen from C₅-C₈ alkyl, C₄-C₈ alkenyl, C₅-C₈
alkoxy, C₅-C₈ alkylthio and phenyl,
in which the phenyl ring is unsubstituted or substituted by
25 a substituent chosen from halogen, trihalomethyl and C₁-C₄
alkyl; or (c) a cyclohexyl or cycloheptyl group
unsubstituted or substituted by one or two C₁-C₄ alkyl
groups;

T is a C₁-C₅ alkylene or C₂-C₅ alkenylene group; or a
30 phenylene group;

X is a bond or a -O-CH₂- group;

R₂ is an -OR₃ or -NHR₃ group, wherein R₃ is hydrogen or C₁-
C₄ alkyl; and the pharmaceutically acceptable salts thereof.

3. A compound of formula (I), according to claim 1, wherein

R is hydrogen;

A is $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}_2-\text{CH}_2-$ or $-\text{CH}(\text{CH}_2\text{Ph})-$ in which Ph means phenyl optionally substituted by a halogen atom;

5 R_1 is a) C_5-C_7 alkyl; b) a phenyl, pyridyl or thienyl ring, unsubstituted or substituted by halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or trifluoromethyl; or c) a cyclohexyl or cycloheptyl ring;

T is a C_2-C_4 alkylene or phenylene group;

10 X is a bond or a $-\text{O}-\text{CH}_2-$ group;

R_2 is an $-\text{OR}_3$ group wherein R_3 is hydrogen or C_1-C_4 alkyl; and the pharmaceutically acceptable salts thereof.

4. A compound selected from the group consisting of the following, either as Z- or E-isomers or Z,E-mixtures of said isomers:

5-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

5-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanamide;

20 ethyl 4-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoate;

4-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

25 methyl 3-[1-phenyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoate;

ethyl 5-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoate;

5-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

30 5-[1-(3-bromophenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

4-[1-(3-trifluoromethylphenyl)-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;

- 5-[1-(3-(n-butyl)phenyl)-2-(imidazol-1-yl)ethyl-
idene]aminoxypentanoic acid;
5-[1-(2-methoxyphenyl)-2-(imidazol-1-yl)ethylidene]
aminoxypentanoic acid;
5 ethyl 3-oxa-5-[1-phenyl-2-(imidazol-1-yl)ethylidene]
aminoxypentanoate;
3-oxa-5-[1-phenyl-2-(imidazol-1-yl)ethylidene]ami-
noxypentanoic acid;
10 3-oxa-5-[1-(3-trifluoromethylphenyl)-2-(imidazol-
1-yl)ethylidene]aminoxypentanoic acid;
tert-butyl 5-[1-phenyl-2-(imidazol-1-yl)-2-methyl-
ethylidene]aminoxypentanoate;
5-[1-phenyl-2-(imidazol-1-yl)-2-methylethylidene]-
aminoxypentanoic acid;
15 3-[1-phenyl-2-(imidazol-1-yl)ethylidene]
aminoxymethylbenzoic acid;
4-[1-phenyl-3-(imidazol-1-yl)propylidene]aminox-
ybutanoic acid;
5-[1-(n-hexyl)-2-(imidazol-1-yl)ethylidene]aminox-
20 ypentanoic acid;
ethyl 5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]
aminoxypentanoate;
tert-butyl 5-[1-cyclohexyl-2-(imidazol-1-yl)ethyli-
dene]aminoxypentanoate;
25 5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]amino-
xypentanoic acid;
ethyl 4-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]
aminoxibutanoate;
4-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]
30 aminoxybutanoic acid;
5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]
aminoxypentanamide;
3-oxa-5-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]
aminoxypentanoic acid;
35 5-[1-(3,3-dimethylcyclohexyl)-2-(imidazol-1-yl)
ethylidene] aminoxypentanoic acid;
5-[1-cyclopentyl-2-(imidazol-1-yl)ethylidene]
aminoxypentanoic acid;

- 5-[1-(2-thienyl)-2-(imidazol-1-yl)ethylidene]
aminoxypentanoic acid;
ethyl 5-[1-(3-pyridyl)-2-(imidazol-1-yl) ethylidene]
aminoxypentanoate;
- 5 5-[1-(3-pyridyl)-2-(imidazol-1-yl)ethylidene]
aminoxypentanoic acid;
4-[1-(3-pyridyl)-2-(imidazol-1-yl)ethylidene]
aminoxypentanoic acid;
- 5-[1-(3-n-butyloxyphenyl)-2-(imidazol-1-yl)ethylidene]
aminoxypentanoic acid;
- 10 ethyl 5-[1-(3-n-butyloxyphenyl)-2-(imidazol-1-yl)
ethylidene]aminoxypentanoate;
6-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]aminoxihexanoic
acid;
- 15 3-oxa-6-[1-cyclohexyl-2-(imidazol-1-yl)ethylidene]
aminoxihexanoic acid;
5-[1-cycloheptyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic acid;
6-[1-cycloheptyl-2-(imidazol-1-yl)ethylidene]aminoxihexanoic
acid;
- 20 5-[1-n-heptyl-2-(imidazol-1-yl)ethylidene]aminoxypentanoic
acid;
5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]
aminoxypentanoic acid;
- 25 5-[1-cyclohexyl-2-(imidazol-1-yl)-2-benzylethylidene]
aminoxypentanoic acid;
ethyl 5-[1-phenyl-2-imidazol-1-yl)-2-benzylethylidene]
aminoxypentanoate;
ethyl 5-[1-cyclohexyl-2-(imidazol-1-yl)-2-benzyl-
ethylidene]aminoxypentanoate;
- 30 6-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene]
aminoxihexanoic acid;
6-[1-cyclohexyl-2-(imidazol-1-yl)-2-benzylethylidene]
aminoxihexanoic acid;

5-[1-(4-fluorophenyl)-2-(imidazol-1-yl)-2-(4-fluorobenzyl) ethylidene] aminoxypentanoic acid;

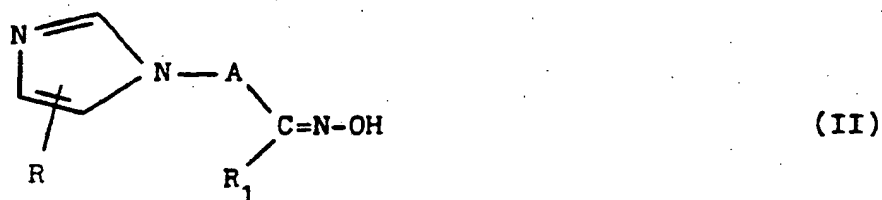
5-[1-cyclohexyl-2-(imidazol-1-yl)-2-(4-fluorobenzyl) ethylidene] aminoxypentanoic acid; and

5 3-oxa-5-[1-phenyl-2-(imidazol-1-yl)-2-benzylethylidene] aminoxypentanoic acid;

and the pharmaceutically acceptable salts thereof.

5. A process for the preparation of a compound of formula (I), or a salt thereof, according to claim 1, the process comprising:

a) reacting an oxime of formula (II) or a salt thereof



wherein

claim 1

R, A and R₁ are as defined in/ , with a compound of formula (III)

15



wherein

claim 1

T, X and R₂ are as defined in/ and Y is a leaving group;
or

- b) reacting an oxime of formula (II) as defined in ^{claim 1} or a salt thereof with a lactone of formula (IV).



wherein

- 5 T and X are as defined in ^{claim 1}, thus obtaining a compound of formula (I) in which R₂ is -OH; or

- c) reacting a compound of formula (V)



wherein

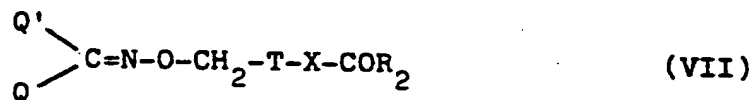
- 10 R, A and R₁ are as defined in ^{claim 1}, with a compound of formula (VI)



wherein

T, X and R₂ are as defined in claim 1; or

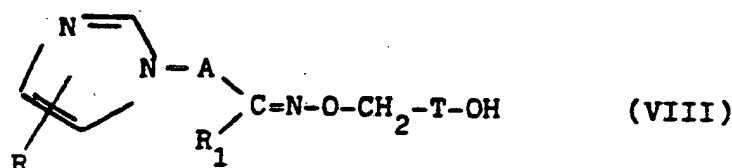
- 15 d) reacting a compound of formula (V), as defined in claim 1, with a compound of formula (VII)



wherein

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in claim 1,

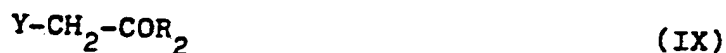
T, X and R₂ are as defined / and each of Q and Q' is independently hydrogen, lower alkyl or phenyl; or
e) reacting a compound of formula (VIII) or a salt thereof



5 wherein

claim 1

R, R₁, A and T are as defined in / , with a compound of formula (IX)



wherein

claim 1

10 Y and R₂ are as defined in / , thus obtaining a compound of formula (I) wherein X is a -O-CH₂- group; and if desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired converting a compound of formula (I) into a salt thereof, and/or, if desired, converting a salt of a compound of formula (I) into a free compound, and/or, if desired, separating a mixture of isomers of a compound of formula (I) into the single isomers, and/or, if desired, altering by isomerization on the oxime double bond the ratio of E- and Z-isomers of a compound of formula (I) in a mixture thereof so as to obtain a different ratio of such isomers, and/or, if desired, converting by isomerization on the oxime double bond a pure E-isomer of a compound of formula (I) either into a pure Z-isomer thereof or into a mixture of E- and Z-isomers thereof; and/
20 or if desired converting by isomerization on the oxime double bond a pure Z-isomer of a compound of formula (I) either into a pure E-isomer or into a mixture of E- and Z-isomers thereof.

25

6. A pharmaceutical composition containing a suitable carrier and/or diluent and, as an active principle, a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof.

5 7. A compound of formula (I) or salt thereof, according to claim 1, for use in the treatment of a disease related to an enhancement of thromboxane A_2 synthesis.

8. A compound of formula (I) or a salt thereof, according to claim 1, for use in the treatment of nephropathies.

10 9. A compound of formula (I) or a salt thereof, according to claim 1, for use in the prevention and/or treatment of cyclosporin A-induced nephrosis.

15 10. A compound of formula (I) or a salt thereof, according to claim 1, for use in the treatment of hyperlipidaemia secondary to nephrotic syndrome.